VOLUME 94 • OCTOBER 1957 • NUMBER 4

# DISEASES OF CHILDREN

Presidential Address—American Pediatric Society
*Daniel C. Darrow*

Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Ethel C. Dunham at the Sixty-Seventh Annual Meeting, June 18, 1957, Carmel, Calif.

Introduction and Presentation by Dr. Harry H. Gordon

Acceptance by Dr. Ethel C. Dunham

American Pediatric Society

Abstracts from Current Literature

News and Comment

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*Ratner, Bret; Crawford, L. V.; and Flynn, J. G.: Amer. J. Dis. Child., 91:593, 1956

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# A. M. A.
# Journal of Diseases of Children

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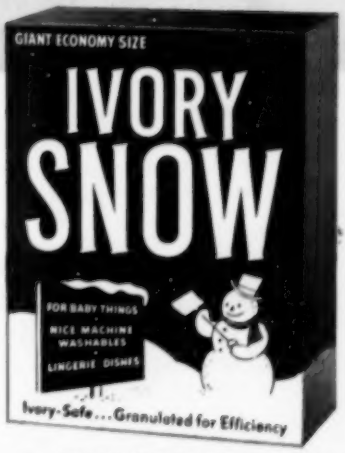


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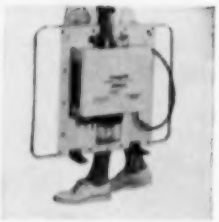

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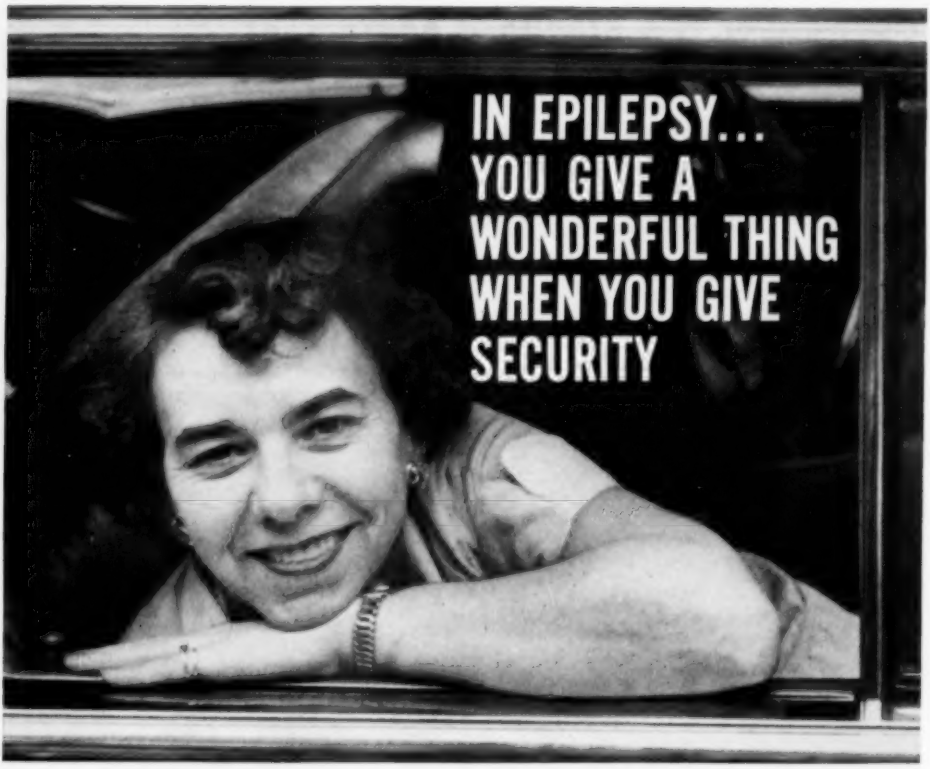


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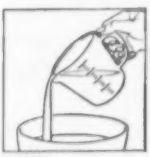

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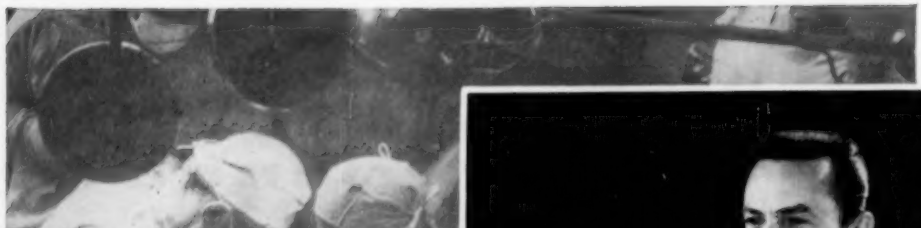

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(1) Smith, N. J., and Rosello, S.: J. Clin. Nutrition *1*:275, 1953.

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# Presidential Address—American Pediatric Society

DANIEL C. DARROW, M.D., Mission, Kan.

Because the majority of the members of the American Pediatric Society are engaged in educating doctors, a president need not apologize for talking on this much-discussed subject. Our faith and practice in education should be repeatedly examined in relation to the changes in society and medical knowledge. My remarks are intended to bring before the Society certain points of view which, I believe, concern our educational activities.

Starting about 75 years ago, an essentially new emphasis in higher education emerged in the United States. The earliest settlers in all parts of the country were concerned with the preservation and transmission of knowledge lest the new society lapse into incoherent barbarism. On the whole, institutions were established that were capable of this function, but little was done to create an atmosphere which facilitated the development of new knowledge by men trained for this purpose. One needs only recall the isolation of Willard Gibbs at Yale to recognize the defects of the universities. He was undoubtedly the greatest scholar of the physical sciences which this country had produced. Yet, his work was hardly recognized until attention was called to it from the Netherlands. The improvement in our universities is indicated by the profound influence such a man would have today. In the nineteenth century, large numbers of Americans went abroad to prepare themselves for advanced studies. In this respect, the country was particularly indebted to Germany. Consequently, the German universities provided many of the ideas that were later adapted to American institutions. The University of Michigan and Cornell had recognized the need of change; Presidents Angel, White, and Eliot doubtless had the vision of the paths which should be followed, but the complete reorganization seemed too revolutionary to be undertaken at once. Because Gilman had no institution to remodel, he had little difficulty in setting the pattern at Johns Hopkins which has subsequently been followed by our universities, old and new, which are concerned with advanced studies. He established Johns Hopkins on the assumption that the chief function of a university is the advancement of knowledge and not preservation and transmission of knowledge. Inevitably, this meant that the University became more interested in training men to study problems than in teaching current knowledge. The heart of the university became the graduate school.

The revolution in medical education stems from this idea. At the time that the Johns Hopkins medical school was established, medical education was in the hands of practitioners, both in the preclinical and clinical departments. With rare exceptions, an un-

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Mercy Childrens Hospital; Professor of Pediatrics, University of Kansas.

necessarily bad job was being done even for such a set-up. It was easier to be admitted to a medical school at this time than to a good college. To improve medical schools, students capable of and prepared for advanced studies had to be selected. Actually, improvement of the quality of students was not very difficult. Nevertheless, medical schools still have to emphasize that our profession cannot be learned by everyone. The acceptance of research in disease as an essential and primary function of medical schools has not been so readily accepted and perhaps will never be fully accepted. Nevertheless, I have little doubt that the majority of the public and the medical profession do support the idea that one of the chief functions of the medical school is advancement of knowledge. It is important for the American Pediatric Society and medical teachers to understand why medical research is an essential part of the preparation of doctors for the practice of medicine. Research is the process by which teachers and students are forced to deal with the lively facts of medical science rather than the rules of a trade. No stuffing of the head with inert ideas fructifies in significant research. Ours is a learned profession in which all who enter must be prepared to deal with new ideas for the rest of their lives.

To illustrate the actual effect of establishing clinical departments as places for the study of disease, I shall attempt to report my own experience. While I am not trained for the sort of historical research which the subject deserves, I was a student at Johns Hopkins when the revolution in medical education was taking place. I have long felt that the department of pediatrics at Johns Hopkins played a more important role in the changes in medical education than has usually been ascribed to it. It accepted advancement of knowledge as the chief function of the department with fewer reservations than medicine or surgery, at least in the beginning. It has had a more direct and profound effect on pediatric departments throughout the country than the departments of medicine and surgery, which underwent the same reorganization in 1913.

Before 1910 the preclinical departments in the better medical schools were organized for the advancement of knowledge. They were no longer dependent on men also engaged in the practice of medicine. Logically, the next step was to convert clinical departments to the same purpose. The advisability of making men engaged in research responsible for running clinical departments was challenged; the opportunity to put this policy into effect was refused by some men who had shown by their interests and work that they might be the ones best suited for the task. It was argued and still is argued that the teaching of current practice should be the chief aim of medical education and that nothing should interfere with the teaching of clinical subjects by those men best acquainted with current practice. None, it was stated, is better prepared for this task than the practitioner. Nevertheless, the Johns Hopkins University had faith in the assumption on which she was founded: she accepted the opportunity to organize the departments of medicine, surgery, and pediatrics so that advancement of clinical science could become their primary function. Subsequent experience has justified this faith. Men engaged in practice have not been excluded from teaching clinical medicine, but evaluation of clinical practice has been better taught in departments engaged in research as well as practice.

John Howland became the first full-time professor of pediatrics in 1913. A children's hospital and laboratory and a small budget were available. When this new kind of department started, an astonishing event occurred. Like bits of iron attracted to a magnet, a large proportion of the future leaders in pediatric teaching and research came to Harriet Lane. Only two of the men were Hopkins graduates. Of course, this is a tribute to John Howland and his ideas, but, even more, it indicates the need of the times for a place devoted to the study of the

diseases of children. While I was a medical student of Johns Hopkins, the following men worked in the department: John Howland, McKim Marriott, Edwards Park, James L. Gamble, Kenneth Blackfan, Grover Powers, and Benjamin Kramer. Samuel Clausen was a house officer. Any list of the leaders in American Pediatrics in the following thirty years would include these men before twice their number was named. More leaders came before Howland's death, in 1926.

From my undergraduate memory of these men, I often wonder what I did as a medical student. I remember distinctly the weekly clinics of John Howland. They were stimulating; the hard seats of the amphitheater prevented physical relaxation; the prospect of pointed questions kept the minds alert. The method of teaching led to the clinics being called, "Professor Howland's Riding Academy." Perversely, I remember best being convinced that the streptococci could have little to do with scarlet fever. The clinics were well attended, perhaps in part because the staff also thought them important and attended. I remember Blackfan as Howland's right-hand man on the wards; Dr. Park was a tall, dignified man whose scholarship we all admired. I have no picture of Powers or Clausen from my undergraduate days. I remember distinctly that Marriott gave lectures on infant feeding from which I got a hearty dislike of infant feeding. I suspect that Marriott unconsciously transmitted his own attitude, for he must have felt that he was teaching a lot of empirical nonsense and that the subject should be rationalized. At any rate, he did devise a simple, almost fool-proof, system of infant feeding as soon as he went to St. Louis. Kramer appeared as an energetic man who, we thought, knew all about chemistry. We were correct in that he realized the importance of micro methods in the studies on infants. James Gamble was hard to fathom, for we did not see how he functioned. He always had the most engaging smile for medical students—me among others, although I am sure that he did not know me. I learned little that would enable me to practice pediatrics, but I did get the idea that it would take two or three years on a good service to prepare for the practice of pediatrics.

Of course, I was vaguely aware of the exciting studies with which these men were occupied. I got the idea that phosphorus was important and even managed to set up the colorimetric method somewhere not in the pediatric department, but I was too ignorant and shy to find out what could be done with a good quantitative method. I had learned that calcium had something to do with tetany and knew that Kramer and Howland had found that serum calcium was low in rachitic tetany. I knew that phosphorus as well as calcium was concerned with the crooked bones of rickets. I do not remember learning that parenteral fluid therapy showed promise of becoming one of the most important therapeutic measures for sick infants. Blackfan had already shown that intraperitoneal saline was beneficial in dehydration. Marriott and Howland, as well as Schloss and Stetson, had measured the reduction in carbon dioxide content of the blood in the acidosis of infantile diarrhea. They had injected sodium bicarbonate intravenously. I had already learned to determine blood carbon dioxide in my second year working with Dr. MacCallum in pathology. I knew nothing of the ideas that were fermenting in Gamble's head and were to appear in the papers written with Ross and Tisdale. All this was to be my life work and I knew practically nothing about it.

What then did I get out of the finest congregation of investigators in pediatrics that has ever come to one department? I know that I caught a feeling of excitement and was sure that the study of diseases of children must be interesting to attract so many first-class men. I know that I felt the exciting things in pediatrics had not already happened, but were going to happen when such men studied diseases of children.

I am not aware that these men more than others at Johns Hopkins convinced me that the greatest challenge in medicine is discovery of new facts. When I was graduated, I wanted to see if I had sufficient talent to advance medical knowledge.

It is not surprising that I chose pathology. Dr. MacCallum had opened the doors to research in my second year by inviting a few students to take part in an experimental problem. We did not really find out much about the effect of injecting hydrochloric acid into dogs. The experiment was well conceived and has been repeated recently by Pitts and associates with modern techniques, giving important results. Although I found pathology interesting, I could not relate it to diseases without knowing more about clinical medicine. I decided to take at least a year as intern in medicine or pediatrics. I only chose pediatrics because Ashley Weech said that I ought to go to New Haven in pediatrics because Park and Powers were such fine men.

Granting that the ignorance of a student is mostly his own fault, universities should be able to remove some of the stumbling blocks to learning. Insofar as my difficulty may have been the fault of the medical school, the following facts are relevant. Originally, pediatrics had been a minor subsidiary of the medical department—the department of internal medicine. At Johns Hopkins, it was only separated in 1909. It was generally recognized that diseases of infants and children were not receiving adequate attention from doctors concerned primarily with adults. The mortality from nutritional disorders, diarrhea, and infectious diseases was appalling. Historically, the pressing medical problems at that time were conceived in terms of disease entities clarified by anatomical studies. Pediatric departments were consequently established to study and formulate the treatment of certain diseases. I do not believe that many doctors at this time thought that infants and children presented special problems because they were infants and children. Rather, these patients were considered to be susceptible to special diseases which merited study. Accordingly, a pediatric department could be regarded as a sort of *ad hoc* committee for the study of certain diseases. If these problems could be solved, the pediatric departments could be abolished or a new *ad hoc* committee set up for the new disease problems which had been recognized. This idea still recurs when diseases which formerly dominated pediatrics have become less frequent. By all pediatricians, if not by all physicians, it is now recognized that infants and children react in a different way from adults to the various challenges producing diseases. Consequently, no limited approach is justifiable. The continuing problems of pediatrics concern the infants and children and not the peculiar diseases from which they suffer. Only by limiting one's attention to diseases can one believe that some other medical discipline can take care of children better than pediatricians. No one is able to study diseases of children better than doctors devoting their lives to observations of sick children of all types. Failure to appreciate this point of view has led medical schools to consider that much of the work in pediatric departments duplicates the work in adult medicine. When I was a student at Hopkins, other than the clinics and lectures, there was no work required by all students in the pediatric dispensary or wards. A good elective course in the dispensary was offered. Because I did not take this course, I had had little chance to learn how infants and children react to disease. I had little contact with the members of the department. The failure to recognize pediatrics as representing a separate field apart from diseases of children probably explains the defective curriculum when I was a student.

The other difficulty involved establishment of channels by which students could learn about and take part in research activity. The teachers had had no experience with this new type of clinical department. They were fully occupied in the laboratory,

the hospital, and the dispensary. They all did their own chemical determinations because John Howland did not believe in the use of technicians. The men were probably not sure of the place of students in clinical research and did not realize that some students should take part in research. These men were quick to learn, as is indicated by the departments which they organized.

The men I have mentioned left Johns Hopkins in 1920 or shortly thereafter. They became the heads of the departments at Washington, Cincinnati, Harvard, Yale, and Rochester. Other men with essentially the same background went to Duke, Columbia, Minnesota, and Vanderbilt. The departments in these medical schools became essentially the same in spirit as the one that they had worked in at Johns Hopkins except that the medical students worked on the wards and in the dispensary. I shall mention certain observations of the two departments in which I worked.

Marriott organized the department at Washington for the study of infectious diseases under Jean Cooke and metabolic diseases with the aid of Jeans and Clausen and, later, Hartmann. Although he had previously been a biochemist, he showed an uncanny ability to understand clinical problems and remove the nonsense from clinical teachings. This is well illustrated by his system of infant feeding. He gave practical courses to practitioners interested in learning more about pediatrics. He instigated some of the pioneer work on which the modern concepts of dehydration are based. The department immediately became a leader.

Park brought Powers, Dunham, Eliot, and Shohl to New Haven. As intern, I was made aware that each case offered opportunities to study diseases. When vitamin D was discovered, Eliot demonstrated that rickets could be abolished by prophylactic use of cod liver oil. It is interesting that Park, who is still studying obscure details of the pathogenesis of rickets, instigated the practical application of the scientific discovery of vitamin D. When Powers succeeded Park, he broadened the research program to include infectious diseases. The study of bacterial and viral infections by Trask was one of the most effective services to medical science started by Powers. However, he was early interested in studying behavior disorders. These problems were investigated first by Putnam and later by Jackson. None could truthfully say that Powers, who was imbued with the spirit of a department devoted to research, did not teach and practice comprehensive pediatrics. It has always interested me that Marriott, the trained biochemist, gave us a practical solution to infant feeding. However, Powers, the consummate clinician, provided the scientific rationalization of the relation of caloric requirement to the proportions of protein, fat, and carbohydrate. Marriott made infant feeding easy, but Powers made me like the subject and enjoy teaching the rationality which he brought out.

You all know the modern departments of pediatrics. Research in diseases of children has become an integral part of the better care of the patients, the teaching of the students, and the training of the house staff. The members of the staff engaged primarily in practice are in constant contact with the scientific basis of practice, while those chiefly occupied with investigation are not isolated from the problems of practice. Pediatricians have been able to bring many disciplines to bear on the problems of infants and children, whether the fields have been biochemistry, bacteriology, virology, public health, psychology, psychiatry, or sociology. By the way, the doctors discovered sociology long before the sociologists discovered medicine. I know of no evidence that concern with research has led to neglect of good pediatric practice. One could be quite optimistic about the future of pediatrics if one were not aware of the perverseness of human nature. Society in the past has often left the high road to progress for a path leading to a morass.

For some time, there has been dissatisfaction with the internship, the first year of postgraduate training. In the past, political influences have attempted to divert and have partially succeeded in diverting this essentially educational experience to other ends. In the interest of local hospitals licenses have been almost limited to doctors trained in hospitals within certain states. At present, the same type of influence may attempt a similar limitation through accreditation of internships. The threat can be made effective throughout all the United States because of the draft. As leaders in education, the American Pediatric Society must recognize the dangers to programs for training men for general practice and pediatrics. Specifically, there is a movement to abolish accreditation of all straight internships. This is a particular threat to the children's hospitals, which could well be made subservient to other hospitals. This would affect adversely not only postgraduate training but also undergraduate education as well.

Most of us would grant that internships need continual reevaluation, both the so-called straight and the rotating internships. It is not a problem to be solved from the point of view of hospitals or groups in practice or services to communities. It is a problem in which the educational aspects of the program should receive the primary consideration. Good education has always required freedom and has never thrived in a straight jacket. Originally, the rotating internships were designed to supplement the limited direct experience with patients formerly prevalent in medical schools dependent on didactic teaching. Subsequently, some internships have become victims of the false concept of education which utilizes multiplicity of experience rather than quality of experience. The most serious difficulties have arisen from considering that postgraduate training is limited to one year. When this philosophy prevails, a rotation through many services in one year is organized. The men are never on one service long enough to get the feeling for the requirements of good practice in even one field. They are likely not to be ready for the supervised responsibility which good training requires. It has been said that the interns of a rotating service are the forgotten men in an educational program which gives the best to medical students and residents. The situation will not be remedied by subjecting all graduates to a defective program. While the straight internships may need broadening, they seldom suffer from superficiality. They have been successful in teaching the criteria by which the practice of medicine can be evaluated and improved. The dilemma can probably be resolved by introducing experiences in different fields of practice in programs extending over two or three years. Such programs could consider the varying interests of the doctor and the communities in which they practice. The best time for rotation will not be the same for all persons or for all types of practice or for all communities.

General medicine, general surgery, and pediatrics are fields of practice that are not narrow in the sense that they shut themselves off from the rest of medical science. In varying degrees, these fields form the basis for other specialties and, in turn, require knowledge in other specialties in varying amounts. The important end to be attained in the first year is an ability to recognize good medical practice in one of the general fields, supplemented with such other experience as does not interfere with this purpose. I know that during the first year after graduation doctors are able to assume the responsibility required for good training in pediatrics. I also know that with the insight into pediatrics gained from 9 to 12 months as intern in pediatrics doctors are better able to get the knowledge from other services that is helpful to pediatricians. Men rotating through pediatrics for a month in the first year seldom learn enough even to provide pediatric orientation for other fields. On the other hand, I have seen a man with four years resident training in

surgery get a great deal out of three months as intern in pediatrics. I know that this man would have benefited by a shorter period because of his knowledge of surgery. I feel that the broad fields like medicine, surgery, and pediatrics require relatively long periods to be effective in the first year of postgraduate training. If only a short experience in one of these fields is planned, it should be taken in subsequent years, when acquaintance with one of the other broad fields has been attained. Only frustration can result from a rigid program in the first year. There is no ideal program based on one year. Any attempt to prescribe one type of experience for all men in the first year will only prevent the development of suitable programs for general practitioners as well as specialists.

I have little to add concerning undergraduate education except to emphasize that pediatric departments must not be set up as *ad hoc* committees for the study of limited problems or education for one kind of practice. The experience of the past thirty years has demonstrated that research in clinical departments has improved teaching of clinical practice. In the organization of departments, it is not possible and probably not desirable for each department to attempt research in many fields. Nevertheless, it seems essential to give critical attention to at least three fields. First, infants and children suffer frequently from infections—perhaps forty per cent of the time in some years. One cannot justify neglect of infections because the mortality is low. The same false reasoning led to the neglect of psychiatry in the past. Infancy and childhood is the time when immunity is acquired. It is our problem to find out how infants and children can be brought through infections with minimal injury. We cannot leave the problems of allergy and acquisition of immunity to departments of medicine and public health. Second, it needs no emphasis that infants and children exhibit physiological disorders which must be studied in children. Third, pediatric psychiatry must accept the challenge to advance knowledge as well as to teach current practice. The problems are going to be particularly difficult because they involve basic physiology and psychology as well as impinge on sociology.

The most talented of the ancient peoples discovered the key to knowledge of the physical world in the number. The search for the number is the search for the mathematical methods for dealing with quantitative phenomena. It always requires abstraction of the important from the unimportant and subjecting it to measurement. It is irrelevant to point out that scientific abstractions do not explain everything. All knowledge is abstract, because the human mind is incapable of comprehending the whole universe. Sociological and psychological research cannot avoid the scientific necessity of abstracting the important from the unimportant in the phenomena studied. Observations must be subjected to the rigors of mathematics. In the simplest form, mathematics is the logic involved in answering a proposition as true or false. If the proposition cannot be answered in this form, it has no scientific meaning.

The second method of advancing knowledge grew out of recognition by the Greeks that what was true for the Greek city state was not true for Egypt and Persia. The Pythagoreans did not find a way to test this kind of truth, which we would deem sociological and perhaps psychological truth. Nevertheless, the Athenians effectively used the best method we have today. Their greatest teacher was Socrates, who never published a paper. The method is simple; every question must be subjected to unindoctrinated scrutiny. This was a difficult teaching for the Greeks to accept, and it is just as difficult to accept today. As a reaction to social instability and fear of change, anti-intellectual movements arise and substitute indoctrination for unindoctrinated scrutiny. This reaction is the chief enemy to scientific interpretation of phenomena. We live in the midst of world-wide anti-intellectual movements attempting

to direct the course of history by propaganda. The aim of propaganda is to get society to accept a system of thought as doctrine by which thought is judged. In the worst form, the unindoctrinated are excluded from positions of power and council. The conservative point of view is a menace to progress only when a system of thought is taught as doctrine which cannot be examined critically. The dangers of communism and fascism are not the development of new ways of organizing society but the terrifying prospect of domination by systems of thought which prevent unindoctrinated examination of the assumptions on which society functions. Similarly, science has no fear of new ideas but of systems of thought perpetuated by indoctrination rather than subjected to the growth which comes from the examination of the assumptions.

It is for this reason that I do not believe that the scientific basis for clinical medicine which has traditionally been taught in the first two years should be given by men deeply involved in clinical practice. Everyone is unconsciously indoctrinated by the profession which he enters. Clinical science must preserve untrammeled access to ideas free from the assumption of clinical practice. This applies to psychological as well as physical sciences. Clinicians do not know what aspects of basic sciences are going to illuminate clinical medicine. Neither do we know how our students are going to practice in the future. We need only recall how much of present medical practice could not have been taught when we were students. We must continually remind ourselves that our students will start practice about seven years after entering the medical schools. Humbly, we must confess our ignorance and try to learn. Our duty to students is to provide as enduring a basis for scientific practice as possible but, above all, to prepare them to evaluate the future developments and select the good from the bad by learning how to recognize scientific observations in clinical medicine.

5847 Howe Drive.

# Presentation of the John Howland Medal and Award of the American Pediatric Society to Dr. Ethel C. Dunham

*At the Sixty-Seventh Annual Meeting, June 18, 1957, Carmel, Calif.*

**INTRODUCTION AND PRESENTATION BY DR. HARRY H. GORDON**

Dr. Darrow, members and guests of the American Pediatric Society: It has been both pleasure and privilege to prepare this citation for Dr. Ethel Collins Dunham, Howland Medalist of 1957.

What manner of person do we honor? All biographical notes are charged with interest, and particularly so are these. Dr. Dunham was born in Hartford, Conn., to descendants of English immigrants who had come to America before 1640. Her family was active in business, and in a book about her forebears written for distribution to the young folk of the family, one may read of a father and mother never heard to speak angrily to each other, of a mother who painted, of manners and ethics taught by example, of only rare and mild punishment for misdemeanors. Every Saturday during the winter, an aunt conducted at her home a working group at which the young cousins, boys and girls, made articles to be sold at a spring fair for the benefit of a welfare organization. "This workshop was fun, never a chore." In this book we find pictures of distinguished looking forebears side by side with that of the family gardener of fifty years' employ, and also an early picture of our Howland medalist at, I would guess, age 6 to 9 months. I know of no psychological tests performable at this age that would have predicted her distinguished career.

Dr. Dunham graduated from high school in 1901 and chose boarding school rather than college for two years. Over a period of the next six years, which included two trips to Europe with her sister and her Uncle Cornelius, described as scholar and inventor as well as business man, the idea of studying medicine began to crystallize. At age 26, with great independence of mind, she reenrolled in the Hartford High School for a course in physics; a year later she entered Bryn Mawr to prepare for medicine. All credit to the 1914 admissions committee at Johns Hopkins for not permitting sex and age to interfere with her entrance to medical school—if admissions committees could regularly show such prescience in estimating motivation, teachers in medical schools would have to spend much less time on the micro- and macromanipulations of curricula which are now agitating medical educators.

Dr. Dunham graduated from Johns Hopkins in 1918 and spent a year as intern at Harriet Lane under Dr. Howland, with Dr. Blackfan as chief resident. Because many members of her class had gone off to the wars before receiving their degrees, there is a story of a delayed graduation celebration when the men received their commissions in France. Dr. Dunham, thwarted by her inability to join the Army, had something major to do with the original planning of this party; the details of the celebration are, I should guess, not suitable for public presentation, and I therefore refer you to one of the participants, Dr. Lawson Wilkins.

In 1917, while a third-year student, Dr. Dunham served in the isolation section of the New Haven Hospital, in a building replete with memories of Dr. James Trask for those of us who came later to the Department of Pediatrics at Yale. In 1919 she returned from Baltimore to become the first woman house officer in the New Haven Hospital, serving both in medicine and in pediatrics. She was appointed instructor in 1920, and that year she gave the pediatric lectures to the medical students. In this same year, Dr. Milton Winternitz, as new dean, sparked a reorganization of the school which brought to Yale Dr. Park as professor and Dr. Powers as associate professor of pediatrics. Here Dr. Dunham was rejoined by Dr. Eliot, her classmate and close friend, who had gone to Dr. Marriott in St. Louis for her pediatric residency training.

Dr. Dunham was a full-time member of the department at Yale as instructor and assistant professor until 1927, in charge of the outpatient department and the newborn nurseries. This supervision of the nurseries was at least initially *de facto* rather than *de jure*, because of an obstetrician-in-chief trained to keep pediatricians at their distance. What pleasure Dr. Dunham must have in knowing that on the foundation of cooperation which she built Dr. Edith Jackson and her colleagues were later able to develop so productive a rooming-in program. And one of Dr. Dunham's many unpublicized contributions was a car that permitted pediatric interns to visit the homes of newborn infants, an educational experience that deserves repopularization. One of her early papers—published in 1923—is entitled: "Appointment System in the Children's Clinic of the New Haven Dispensary"—then as now, adequate time for each patient is still necessary to permit translation of knowledge of either emotional or physical ills and development into good pediatric care.

From 1927 to 1935 she was associate clinical professor, serving also as medical officer, in the U. S. Children's Bureau in charge of neonatal studies at New Haven. She thus worked intimately in the department of pediatrics at Yale for 16 years and had the opportunity, in her own words, "to see the pediatric department before and after birth, during the neonatal period and after its attainment of maturity."

In 1935 Dr. Dunham moved from New Haven to Washington, where Dr. Eliot became assistant chief of the U. S. Children's Bureau and Dr. Dunham, director of the Division of Research in Child Development. In 1940 she became consultant in pediatrics to the Bureau, a maneuver that permitted her to work full-time for U. S. children while her previous salary was used for other needs of the Bureau. This action was prompted by congressional parsimony with respect to the Bureau, which was being asked to administer a constantly enlarging program for mothers and children. Until 1950 she remained a lecturer in pediatrics with the rank of associate professor at Yale, returning regularly to speak to students and staff. From 1949 to 1952 she served as medical consultant to the World Health Organization with headquarters in Geneva. Since 1952 she has been so-called "retired"—first in Washington and now in Cambridge, Mass.—and you will soon hear of what currently agitates her leisure. Three final items of interest—Dr. Dunham has served as an alumnae director of Bryn Mawr, as a member of the U. S. Civil Service Commission Fair Employment Board, and as state chairman for the Academy of Pediatrics in Connecticut.

So much for the scenes of her activities. What is the contribution to pediatrics that this society has chosen to honor? Primarily it is her work for newborn infants. Early papers from New Haven had as subjects rickets in a 34-day-old infant, syphilis, atelectasis, septicemia, multiple ulcers of the stomach, ruptured stomach, cyanosis, intracranial lesions, and a roentgenographic study of the thorax, all in newborn infants. There were additional articles on tubercu-

losis and congenital syphilis, and a classical review article on the latter subject with Whipple, but in 1936 there appeared her first statistical study, with McAlenney, of prematurely born infants.

From this time on, Dr. Dunham was influenced by statistical data to try to increase fetal salvage. She perceived the opportunities for research offered by collection of such information, and from her Children's Bureau vantage point she saw the issues in large perspective and as a public health problem. Furthermore, because of her warmth as well as clinical experience, mortality statistics represented dying babies and bereaved parents, never just figures on a chart. Her broad social interests led her to want the chances for survival to be as good in New Mexico as in Connecticut. I know she lifted my sights, and probably those of many others, from our immediate interests—mine were at the time in the air-conditioned sub-sub-basement of the New York Hospital—by tales she brought of home and hospital visits made by herself or field representatives of the Children's Bureau—nurses, social workers, nutritionists, doctors. She attacked the problem from several angles: One must spread more widely what was already known about care of the newborn; one must make it possible to apply these facts; one must learn new facts.

To spread knowledge more widely Dr. Dunham lectured and published papers on the appraisal of the newborn infant, on methods of care of the premature infant, on reducing the hazards of the first two days of life. She recognized the importance of trying to prevent premature birth or at least of mitigating its degree. Instead of carping about the group in which the causes of prematurity were not known, she stressed conditions such as infections, toxemia, heart disease, and overwork, proper handling of which would diminish the problems of prematurity. All this culminated in her book, "Premature Infants, A Manual for Physicians," an invaluable asset for all who teach or wish to learn about the newborn. As a measure of our medalist, I read the inscription on the fly-leaf, taken from Ballantyne: "In writing the book I have honestly tried to avoid the four grounds of human ignorance set forth so long ago by Roger Bacon: trust in inadequate authority, the force of custom, the opinion of the inexperienced crowd, and hiding of one's own ignorance with the parading of a superficial wisdom."

How to get wider application of best practices? Dr. Dunham pushed for simple plans of collecting data on neonatal deaths in hospitals and public health departments. I remember a meeting of an early New York City committee convened by Dr. Leona Baumgartner with Drs. Katherine Merritt and Hugh Chaplin as leading members, and Dr. Dunham telling us that if we would only collect data, mortality would start to fall without any great changes in what we were doing. No suggestion was made that the mortality statistics be used as a guide to punitive action; there was none of the self-righteousness which precedes a fighting stance, just a faith that professional personnel who recognized what was happening in their bailiwicks would substitute increased care for rationalizations that premature infants could not be saved or would not amount to much anyhow. Dr. Dunham's respect for people's feelings and local mores made her a master in committee meetings of what is now artfully labeled group dynamics.

Because all the good will in the world would not take the place of adequate facilities, she turned to interested architects, the Tesones, for help in the planning of good nurseries. The Tesones are now her personal friends, a relationship which has developed for many who have worked with her. Their blueprints are familiar to many of you in the standard plans for nurseries used by the Public Health Service in their recommendations for use of Hill-Burton funds. And, as Dr. Stewart Clifford has pointed out, the mimeographed sheets which Dr. Dunham prepared with Dr. Marian Crane and other Children's Bureau col-

leagues became the basis of one of the American Academy of Pediatrics best-sellers: "Standards and Recommendations for Hospital Care of Newborn Infants, Full Term and Premature." Incidentally, during the depression years she turned to the National Youth Administration and had constructed some simple open incubators that cost about fourteen dollars.

All of this concerned hospital care—it had to do with trying to bring benefits of a premature infant center like that which Dr. Julius Hess and Miss Evelyn Lundeen had organized at Michael Reese to a greater number of institutions. But Dr. Dunham went a step further. Reflecting the comprehensive views of child care which have always been the ideals of the Children's Bureau, and which were so well exemplified by Miss Lenroot and Dr. Eliot, respectively then chief and assistant chief of the Bureau, Dr. Dunham sent a public health nurse and social worker from the Bureau's field staff to the New York Hospital in the late 1930's for a six-month period. Their purpose was to make sure that infants given hot-house care in the nurseries of the New York Hospital were not discharged to impossible home environments. The Children's Bureau representatives remained for only six months, but this was long enough to work out the methods, subsequently described by Dr. Hedwig Koenig, by which social workers, nurses, and pediatricians of the New York Hospital have continued for twenty years now to work with public and private social agencies for the continuing benefit of premature infants. All those who have attended the New York Hospital Institutes on premature infants recognize the emphasis on teamwork between doctor, nurse, and social worker, inside and outside the hospital; this is social medicine at its best, and its development in the pediatric department at the New York Hospital was speeded by Dr. Dunham and her colleagues of the Bureau. Those who work in universities are apt to think of government agencies only as sources of funds—the Children's Bureau has always supplied ideas and standards as well. In honoring Dr. Dunham, we recognize the contribution of a group of devoted public servants, many with a "passion for anonymity," who as members of the staff of the Children's Bureau have not only improved the health of children but have also held before us constantly the concept that may be expressed, paraphrasing Terence: "Nothing that has to do with a child is foreign to our interest."

As already mentioned, Dr. Dunham early stressed the importance of obstetric factors in premature infant mortality and refused to be discouraged by obstetricians more aware of their ignorance than of their knowledge and by pediatricians who found it difficult to work with uninterested obstetricians. But this has changed too, and major contributions are coming, as they should, from obstetric departments. At the University of Colorado Dr. Dunham's teachings became the basis for the premature infant program of the State Health Department, which supplies not only twenty beds for premature infants but also three beds for obstetric patients with complications of pregnancy which may lead to premature delivery. The development of obstetric cooperation in premature infant programs around the country is really overdue, and pediatricians should recognize that there has been a favorable change in the attitudes of some obstetricians who may have hitherto appeared unapproachable.

Finally, what has Dr. Dunham achieved for the third part of her program, the need to increase our knowledge of newborn infants? Her own clinical studies in New Haven, her statistical studies in Washington, her studies of the safety of incubators are all direct contributions. With Drs. Christie and Jenss she helped define the validity of using roentgenograms of the long bones as a criterion of prematurity. The modest funds she had at her disposal in 1937 to help expand research on the newborn at the New York Hospital were most welcome and most valuable; they are a far cry from,

but nonetheless the forerunner of, the millions now spent by the National Institutes of Health in this area. Those members of the audience who review applications for the N. I. H. Study Section on Human Embryology and Development carry their responsibility with due regard for those principles of Dr. Howland which have always guided Dr. Dunham and the Children's Bureau—concern for high standards of performance and desire that there be a good return on the dollar. One of the obvious results of Dr. Dunham's devotion to the cause of the newborn infant is the large number of investigations now being conducted in this field—witness that in the combined programs of our two societies no less than twenty-three of sixty-four papers to be read concern themselves with problems of the newborn. Thirty per cent of the papers chosen for presentation before the senior society and forty per cent of those before the junior society are assurance that Dr. Dunham has built well.

Just a few words about Dr. Dunham as a person. She is a writer of furious but unsent letters to the editor; she gardens and paints landscapes now that she has given up golf; she is a good companion because of her sense of humor and greatness of spirit; she distributes her largesse unobstrusively and believes in social action in accord with Maimonides' dictum "to anticipate charity by preventing poverty"; in all her waking moments, she practices Schweitzer's "reverence for life," and her selfless devotion to causes outside herself has made her, to quote Dr. Park, a moral force in both pediatrics and public health.

In a recent issue of the New York Times book review section, an editor states that the aims of art are well expressed by a line from a poem by Wallace Stevens: "But play, you must, a tune beyond us yet ourselves." And this characterizes what Ethel Dunham has meant to her colleagues.

And so to you, Dr. Ethel Collins Dunham, gracious first lady of American pediatrics, doctor of science *honoris causa,* holder-on-high for newborn infants of a torch raised by Boudin and Ylppö, exemplar of steadfastness and devotion, in honor of your contributions as teacher, investigator, and public servant, the American Pediatric Society presents the Howland award for 1957.

Dr. Darrow, Dr. Gordon, and other members of the American Pediatric Society, I am sure that you appreciate the humility with which I accept the Howland Award. My indebtedness is very great to Dr. Howland, who aroused my initial interest in pediatrics in my student days and deepened it during my service as an intern on his staff at the Harriet Lane Hospital in Baltimore.

Dr. Ethel C. Dunham

Now, with a retrospect of nearly forty years, I shall not dwell on the past but will, in my current role of a library researcher, present some evidence of what I hope you will regard as a look into the future.

What can we do to further the knowledge of the problems of premature birth? There are, of course, many pediatricians who are now involved in this area of research, as witness the ever-growing volume of reports in the medical literature. Yet, as I have observed the trends of research and the methods used, doubts have arisen in my mind about whether it is justifiable to use these infants for experimental purposes. As you all know, the more immature the infant, the greater the need for research and, conversely, the less the ability of the infant to withstand the sometimes traumatic procedures involved. Could not the prematurely born young of some animal be substituted for the human young or for the mature animals now used for research in this field? If so, what animal would be suitable?

With these thoughts in mind I called, more than a year ago, on Dr. William Mann, a distinguished zoologist of the Smithsonian Institution and the then Director of the National Zoological Park in Washington, D. C. In answer to my question about a mammal that gave birth to liveborn offspring prematurely, he stated that the marsupial is the only such mammal and that the opossum is the only marsupial on the North American continent. He pointed out, however, that the birth of the opossum young is not premature in a strict sense. Although the young are born in the embryonic stage of development, this is a "normal" procedure for the opossum and, I might add, a fortunate one, I think, for research on problems of human premature birth. Before elaborating this subject, I must provide what is commonly known as "background material."

I wonder whether you are aware that the American opossum is a primitive mammal that has been referred to as "a living Cretaceous fossil" because it developed to its present form in that geologic age millions of years ago. The name "opossum" was coined from the Indian word for this animal by Captain John Smith, a founder of Jamestown, Va. Hence the American opossum, wherever it is found in North America today, is known as the Virginia opossum.

The natural habitat of the opossum is the eastern half of the United States, and

Fig. 1.—Portrait of the Virginia opossum, the woapink or "white-face" of the Lenape Indians. (Reproduced from Hartman, University of Texas Press, Austin, Texas.)

from there the opossum has spread into Canada and has been introduced into some of the western states also.

The Virginia opossum is a small furred omnivorous mammal which varies greatly in size. The mature female weighs between 900 and 2700 gm. (2 and 6 lb.), the average being about 1350 gm. (3 lb.).

The chief external features of the opossum were graphically described in 1616 by an English traveler to this country as follows:

> The opossum hath a head like a Swine, a tayle like a Rat, [is] as big as a Cat, and hath under her belly a bag, wherein she carrieth her young. . . . It hath the bodie of a Fox [and is] handed and footed like a Monkey.

Figure 1 is a rather flattering portrait of the opossum, showing the sharp, pointed snout and the long stiff whiskers, but not the long hairless tail or the sharp, pointed teeth, which, when exposed, give it a fox-like appearance. The monkey-like foot with an opposable clawless thumb is shown in Figure 2, and Figure 3 shows the marsupium—the abdominal pouch—snugly filled with the 10-week-old young.

The internal structure of the opossum has unusual aspects also. There are two uteri and two ovaries, as shown in Figure 4. The opossum has no placenta. According to Hartman, the amnion fits close about the embryo, and the chorion with its blood vessels is in close contact with the uterine wall of the mother. Thus food and oxygen are supplied to the embryo, and waste products are excreted by way of the maternal blood stream.

During the intrauterine period of 13 days between copulation and parturition the growth and development of the various body organs is so rapid that McCrady not only reports his findings for each of the 13 days

Fig. 2.—Left hind foot of the opossum, with opposable clawless thumb. (Reproduced from Hartman, University of Texas Press, Austin, Texas.)

involved but describes in detail 35 developmental changes within these 13 days.

The labor and birth of the opossum young has been observed and recorded by Hartman. The pregnant female sits on her haunches and licks the vulva and the interior of the pouch to smooth its hairy lining. In the same way, she smooths a path from the vaginal opening to the pouch.

After the embryonic young—numbering a dozen or more—are born, the mother removes the remnants of the membranes ruptured during parturition and licks up the fluid, in which her offspring might otherwise drown.

Figure 5 is an enlarged photograph of the newborn opossum. At this time it is between 11 and 16 mm. long and weighs between 0.1 and 0.2 gm. To visualize the actual size, think of a Boston baked bean or a bumble bee. Note that it is hairless and that the forelegs are functional, with well-developed claws, in contrast to the hind legs, which are nonfunctional fetal pads.

The next event is the migration of the embryonic young to the pouch, which Hart-

Fig. 3.—The pouch, snugly filled with the young. (Reproduced from Coghill, *The Ohio Journal of Science*, Ohio State University, Columbus.)

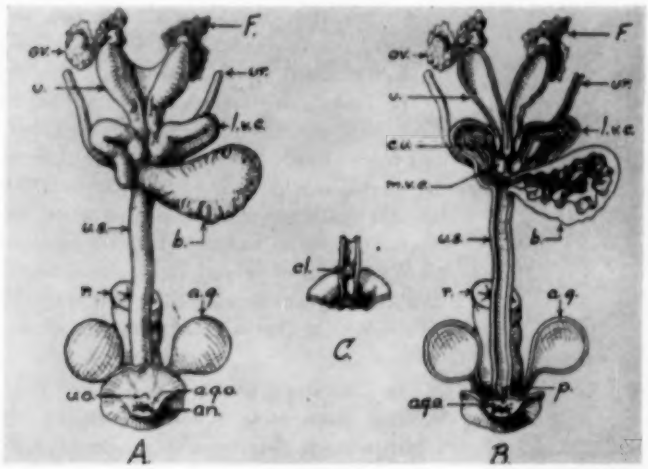


Fig. 4.—Adult female urogenital system in anestrus condition. *A*, ventral view. *B*, dissection of the same specimen. Note the completely double uteri. (Reproduced from McCrady, Wistar Institute of Anatomy and Biology, Philadelphia.)

man's observations have shown to be a journey undertaken without maternal assistance. The direction taken by the newborn young toward the pouch is said to be a "true tropism," or simple automatic orientation, conditioned solely by the structure of the body at the time. The distance traveled from the birth place to the pouch is about 7.5 cm., which is more than five times the length of the embryonic traveler.

The opossum young are well-prepared for pouch life. On entering the pouch, they find the teats, which are about the size of the head of a common pin. Upon entrance into the mouth, the tip of the teat expands to form the so-called oral plug, shown in Figure 6. Thus the young are securely anchored, and a continuous flow of milk is assured.

The young breathe at birth, although the lungs are incompletely developed, having no "true" alveoli at this time.

Figure 7 shows a dissection of the abdominal viscera of the opossum on Day 1. The intestines have been removed to show the stomach, which has become "enormously" large immediately after birth from distention with milk. Heuser pointed out that the stomach "glands are nowhere present, nor can any of the elements be regarded as cells associated with the formation of acid as found in the functioning stomach of higher mammals." The stomach, therefore, is a reservoir at this time and does not

Fig. 5.—The newborn opossum. (Reproduced from McCrady, Wistar Institute of Anatomy and Biology, Philadelphia.)

Fig. 6.—Section from an 8-day postpartum opossum shows the expanded tip of the teat in its mouth. (Reproduced from McCrady, Wistar Institute of Anatomy and Biology, Philadelphia.)

Fig. 7.—Dissection of the abdominal viscera of the opossum on Day 1. The intestines have been removed to show the stomach already distended with milk. (Reproduced from Heuser by McCrady, Wistar Institute of Anatomy and Biology, Philadelphia.)

otherwise participate in the digestive process.

The intestines have been transformed, only five days before birth, from the primitive gut to a functioning alimentary system. Digestion of milk takes place largely in the small intestine, in all parts of which the villi are present. The large intestine, on the other hand, has changed little in the transformation from the embryonic to the pouch-young stage. Heuser found that "the relatively slight dilation of the colon and the histological findings indicate that the residue of the foodstuffs reaching the colon in the opossum pouch young is relatively small; practically all of the milk must be disposed of in the upper portions of the alimentary canal."

At the end of about 50 days after birth all of the organs have reached the stage of development approximating that of most newborn placental mammals.

Before going on to discuss some of the specific advantages of the use of the opossum in research, I want to tell you how we happen to have available an animal so remarkably suited to this purpose.

The evolution of the opossum and other marsupials to their present form occurred, as I have already pointed out, some time in the Cretaceous period, 60,000,000 to 130,000,000 years ago, about the time when the dinosaur became extinct. But the marsupials have survived and have not changed in all these years because they were adapted to survival in that age, as they are in the present age.

The ancestors of the marsupials were evolved from some branch of prehistoric reptilian stock. Figure 8 shows the similarity in skeletal structure between that of an extinct mammal-like reptile and that of the American opossum.

Barrett has pointed out that "countless ages ago marsupials were widely spread over Europe; indeed Australia derived her characteristic animals from the Old World before land-bridges disappeared in the depths of the sea." The theory is that their precursors traveled on floating logs and debris over the seaways from one land area to another.

The oldest known fossil, which was classified as that of a marsupial of about 100,000,000 years ago, was found in Montana and was described by Matthew in 1916. This fossil and those found elsewhere in the western part of North America show a close similarity with the Virginia opossum of today. The evidence points strongly to America as the original home of the marsupials, which are now found only in the Americas and in Australia. Their presence now in Australia, as the only native mammals, is explained by the isolation of this continent for millions of years, with the consequent absence of competition from higher types.

The North American opossum differs in some structural details from the species in South America and in Australia, but, as already pointed out, they all have a common ancestor.

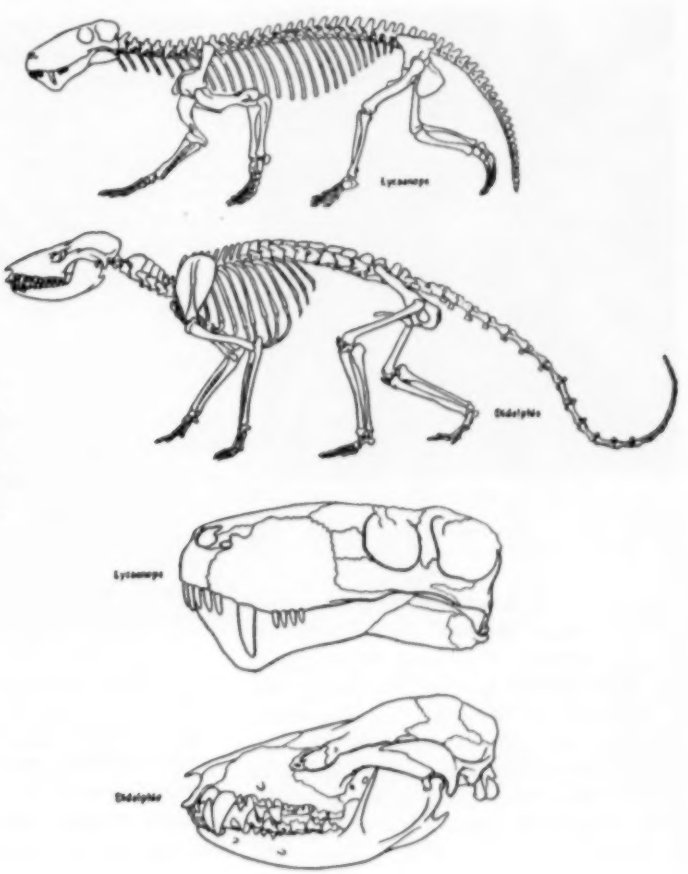


Fig. 8.—Comparison of skeletons and of skulls of an extinct mammal-like reptile and of a primitive living mammal—the opossum. (Reproduced from Simpson, Yale University Press, New Haven, Conn.)

I shall now consider the question of the opossum's role in research into the problems of human premature birth. In the first place, an enormous amount of research has been done on the developmental anatomy, embryology, neurology, and endocrinology of the opossum in the prenatal period. In his monograph published in 1938, McCrady reported his own work and included an exhaustive review of the literature. This work and that of later researchers in these fields provide a solid background for future research of a clinical nature.

Secondly, the young, while living in a favorable environment and being properly fed, are easily accessible for research at each stage of development.

In regard to the environment, the temperature within the pouch is according to Hartman "presumably higher than that of the unoccupied pouch by virtue of the rich blood supply of the actively secreting mammary glands."

The air within the closed pouch was found by Reynolds to have a $CO_2$ content that ranged between 2% and 6%, compared with that of 0.03% for outside air at sea level. The $CO_2$ content of the pouch increased as the young grew larger, as would be expected to result from overcrowding the pouch.

A third advantage for research work is the anchorage which the teats provide and the elongation of the teats with the traction

Fig. 9.—A photograph of the young opossums being drawn forcibly from the pouch to show extensile teats. (Reproduced from Coghill, *The Ohio Journal of Science*, Ohio State University, Columbus.)

of nursing. The length of the teats is said to double within one hour after attachment, and they continue to elongate during pouch life. With careful handling the young may be lifted out of the pouch for operations, injections, and other procedures. If accidentally detached from the nipple, they will reattach themselves when replaced in the pouch. Figure 9, taken from above, with the mother lying on her back, shows the extensibility of the teats when the young are being forcibly withdrawn from the pouch.

Another advantage that the opossum young affords the researcher is that all of the litter of 11 or 12 young are in the same stage of development, so that some may be used as control material. In addition, since the young remain in the pouch for some 50 days, continuous observations are possible over a relatively long period of time.

As has been pointed out already, the opossum is commonly found in many areas of this country, and it can be raised and bred in captivity, provided that a close approximation to its normal habitat is maintained and that the diet is suitable.

Failure to use the opossum in pediatric and other medical research may be due to some of the following factors: It cannot be domesticated, has sharp teeth, and is relatively expensive to feed compared with rabbits and mice. However, none of these are insurmountable obstacles to its use today. In my opinion, heed should have been given long ago to the advice of the famous French naturalist, Buffon, who pointed out 200 years ago that the study of the opossum's postnatal development could be useful by "indicating to us some way of preserving the lives of prematurely born infants."

A few examples of research on the opossum already reported or in progress will indicate some of the possibilities for research related to human premature infants.

In the first place, the rate of growth of the pouch young has been determined. The first study was made by Hartman, who measured and weighed 68 young animals of both sexes still under the protecting care of the mother. He pointed out that his plotted curve of snout-rump length in millimeters on weight in grams had the usual shape of length-weight curves and that this curve resembled Streeter's curve based on measurements of human fetuses.

Later, Moore and Bodian compiled similar data for 55 opossum pouch-young during the period from birth to 75 days. Their growth curves, based on unsmoothed averages, are shown in Figure 10. Please disregard Curve *B* (head-length). Curve *A* shows the increase in snout-rump length in millimeters, and Curve *C*, the increase in weight with age. During the period of observation the length increased more than 7 times and the weight, about 260 times.

The establishment of these curves affords the opportunity to study in the opossum the effect on growth of various agents administered to them and then to apply to the premature infant the knowledge thus obtained. For example, the composition of possum * milk at various stages of development of the young in relation to their rate

* The Australian brushtail phalanger or possum (Tricosurus vulpecula).

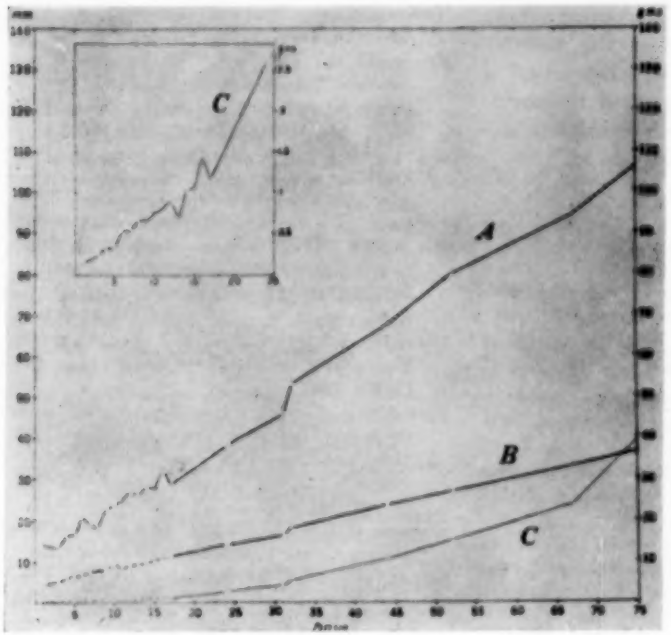


Fig. 10.—Growth curves of 55 opossum pouch-young from birth to 75 days. *A*, unsmoothed averages of snout-rump length; *B*, head length; *C*, weight. (Reproduced from Moore and Bodian, *Anatomical Record*, Wistar Institute of Anatomy and Biology.)

of growth is currently the subject of a study by Bolliger and Gross in Australia. Preliminary analyses show that, generally speaking the protein, fat, and ash content is higher than in human milk. An interesting finding in an analysis of kangaroo milk by Bolliger and Pascoe was that the fat content increased with age. Such studies may throw additional light on the still controversial problem of suitable feedings for the premature infant at different stages of development.

In this connection, it is my opinion that the weakest link in the chain of research on premature infants is the failure to study them at different stages of development. It would be presumptuous for me to point out specific problems that might be attacked in this way, but I would like to suggest one example of research that might be furthered by using the opossum. This concerns the adrenal gland, which is a subject of current pediatric interest. One approach to the problem has been the use of sections of the bodies of human fetuses to determine the development of the parts of the gland and to relate them to particular functions. In the opossum we have a living abortion, born at the time of the earliest developmental stages of this gland. According to McCrady, the cells that are the anlage of the cortical portion of the gland appear just before birth (on the 11th and 12th days), and on the day of birth (the 13th day) the medulla is in the process of formation from chromaffin cells. This degree of cortical development in the opossum corresponds with that of the 4- to 5-week-old human embryo, and the degree of medullary development, with that of the seventh-week human embryo. It is of course true that the young of various animals have been used in research on the adrenal gland, but as far as I know none have proved entirely satisfactory, for one reason or another. The advantages of exploring the use of the opossum in this type of research seem fairly obvious.

I hope that perhaps I have now stimulated your interest in opossums as research animals and that some of you may wish to undertake research using them as subjects

rather than the human premature infant. The problem is how to obtain material. My next interest, if the demand arises, is to see that a farm is organized to provide these animals for research. I like to call myself the "apostle to the opossum."

21 Francis Ave., Cambridge 38, Mass.

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# Society Transactions

## AMERICAN PEDIATRIC SOCIETY

**Sixty-Seventh Annual Meeting, Carmel, Calif.**

**Dr. Daniel C. Darrow, President**
**Dr. Samuel Z. Levine, Vice-President**
**Dr. Hattie E. Alexander, Chairman of the Council**
**Dr. Alms C. McGuinness, Secretary-Treasurer**
**Dr. Stewart H. Clifford, Recorder-Editor**
**June 17-19, 1957**

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   Robert A. Good, J. B. Aust,* Carlos Martinez,* Richard H. Egdahl,* and Richard L. Varco *
3. Epidemiologic Characteristics of Certain Phage Types of Staphylococci in a Newborn Nursery
   Thomas E. Shaffer,* Jack N. Baldwin,* Robert F. Sylvester,* Melvin Rheims,* and Warren E. Wheeler
4. Defects in the Biosynthesis of Thyroid Hormone in Congenital Goitrous Cretinism
   H. David Mosier * and Robert M. Blizzard *
5. Stable Iodine Measurement in Plasma, Thyroid, and Urine in Hypothyroidism, Colloid Goiter, and Hyperthyroidism
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6. Indications for Oxygen Therapy in Small Premature Infants
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7. The Health of the Ex-Premature: A Field for Further Study
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8. Metabolic Studies of Infants Fed Pasteurized and Fresh Human Milk
   Samuel J. Fomon * and Charles D. May
9. Intake of Linoleic Acid in Relation to Serum Unsaturated Fatty Acids and Fat-Deficiency Symptoms in Infants
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11. The Prognostic Implications of the Estimation of the Severity of Childhood Nephrosis
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13. ECHO Viruses Associated with Respiratory Disease in Children
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14. Relationships of Measles and Distemper: Pathological and Immunological Data
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15. Experimental Transmission and Trials and Passive-Active Immunity in Viral Hepatitis
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17. Rumination—A Psychosomatic Disorder of Infancy
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19. Insulin-Producing Capacity of the Pancreas in Children with Diabetes Mellitus
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* By invitation.

22. The Treatment of Paradoxical Hypertension and Necrotizing Arteriolitis Following Resection of Coarctation of the Aorta
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23. The Effect of Exercise on Left-to-Right Shunt of Blood Through a Ventricular Septal Defect, as Shown by Dye-Dilution Curves
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24. The Natural Transformation of Ventricular Septal Defects into Ventricular Septal Defects with Pulmonary Stenosis and/or into Tetralogy of Fallot: Clinical and Physiologic Findings
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27. Behavior of Young Children Under Conditions Simulating Entrapment in Refrigerators
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70. Identification of Enteropathogenic Escherichia Coli by a Microprecipitin Method Specific for the B Antigen
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* By invitation.

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77. Effect of Diethylstilbestrol on Growth and Skeletal Maturation in Adolescent Girls with Tall Stature
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78. Chromosomal Sex in Disorders of Sex Development
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79. Gynecomastia and Stromal Hyalinization in a Young Boy
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**Gastric Contents in Primary Tuberculosis.** SAUL BLATMAN, M.D.*; GARRISON RAPMUND, M.D.*; DONNA NEWSTRAND, B.S.*, and HATTIE E. ALEXANDER, M.D., New York.

As a member of the national cooperative study planned to determine whether early treatment of asymptomatic primary tuberculosis with isoniazid (INH) (4 to 6 mg. per kilogram) for one year will prevent tuberculous meningitis, we have studied 106 children, the majority of whom are under 2 years of age and the rest under 3 years. Our interest in the influence of isoniazid therapy on evolution of the primary complex led to a study of the sensitivity of the available criteria for assessment of the tuberculous infection.

The only requirements for admission to the study were age less than 3 years, more than 5 mm. of induration and erythema after intracutaneous tuberculin (PPD or OT), and absence of symptoms. Before assignment to the study each patient was admitted to Babies Hospital for assessment of the tuberculous infection. Gastric contents, blood, and spinal fluid were cultured for tubercle bacilli; the ESR was determined; the spinal fluid was examined for cells and concentration of sugar and protein; the lungs were examined by x-ray, and the patient was observed. Initially all biologic fluids in all patients failed to grow tubercle bacilli and only 25% showed signs on x-ray of the lungs suggesting a primary complex. Therapy was carried out at home, and the children were examined in our outpatient department at monthly intervals; temperature and weight were recorded, and on some visits an x-ray of the lungs was taken.

After cessation of isoniazid or placebo treatment at the end of one year, the above observations continued and gastric contents were cultured for the second time. Of 69 patients in whom these studies have been completed, 21.7% have grown tubercle bacilli from the gastric contents, which have produced typical lesions in guinea pigs. In order to avoid bias in assessment of the clinical progress and need for treatment in the future handling of our patients, we have not demanded to be informed which patients have had isoniazid and which a placebo. We know, however, that 33% of those with positive cultures received isoniazid and the remainder, placebo. Examination of the sensitivity of these strains revealed that in 60% of the patients the tubercle bacillus populations were considered sensitive to isoniazid and in 40% there was a range from moderately sensitive to resistant. Those children from whom tubercle bacilli were grown were asymptomatic and did not differ from the other children in the study as judged by x-ray examination, ESR, weight gain, general clinical condition, or degree of tuberculin allergy. It was discovered that after 1 year 40% of the children with positive gastric contents had negative skin tests and at 18 months 36% were negative to 1.0 mg. of OT. These percentages are approximately the same for skin tests of all children under study.

The results suggest that microbiological examination is a sensitive index of the state of the primary tuberculosis lesion. Whether these findings reflect the inadequacy of the dose of isoniazid or the fact that this therapeutic agent cannot alter the future hazard of chronic pulmonary tuberculosis in these patients because it cannot eliminate the tubercle bacillus can not be answered at present. The significance of the large number of negative skin tests remains to be explained by long-term follow-up of these patients and by learning which patients received isoniazid.

### Discussion

DR. STUART S. STEVENSON, Pittsburgh: I should like to ask how many of the subsequent nonreactors to old tuberculin were originally tested with old tuberculin and how many with PPD.

DR. HORACE L. HODES, New York: Was the correlation different when 10 mm. of induration was used as a limit for positivity of tuberculin? There has been some question about the nonspecificity of reactions at 5 mm.

DR. HATTIE E. ALEXANDER, New York: I think these surprising results may be only a reflection of the fact that modern microbiological methods are just beginning to be used in the study of the natural history of tuberculous infection. I think it is pretty clear that it is the most sensitive index of the state of the lesion. However, the interpretation of our results must certainly await a long-term study of the evolution of the lesions in the patients in this group.

* By invitation.

The presence of tubercle bacilli in the sputum of well children emphasizes a principle which I think deserves comment because it is now pretty well established. Even though modern antituberculous therapy has been striking in its effect in acute infection due to tubercle bacilli, it is quite clear that there has been virtually no influence on the incidence of adult chronic pulmonary tuberculosis. There are many who feel that this is the number one infection, even in this country, in which tuberculosis is relatively not too important a problem. For example, Dr. Dubos brings out the fact that it is about 10 times greater a problem, both morbidity-wise and mortality-wise, than poliomyelitis, which we all recognize as such an important problem.

There is reason to believe that if the tuberculous lesion has progressed to necrosis the tubercle bacilli, provided, of course, that the resistance of the host is good, will become inactive metabolically. The chemical reaction around the lesion is part of the host's defense mechanism. However, this partially defeats or certainly limits the efficiency of antituberculous therapy.

It is now well established, in vitro as well as in patients, that elimination of the tubercle bacillus by the bactericidal action of therapeutic agents occurs only when the organisms are actively multiplying.

If treatment is applied only after necrosis has occurred, there is reason to believe that tubercle bacilli will persist in the lesion regardless of the therapy and provide a potenital nidus for emergence of acute disease later in life, provided, of course, that the factors, most of which are unknown, that control resistance are altered. There are many who believe, and I think this deserves comment, that prevention of adult chronic pulmonary tuberculosis is the responsibility of the pediatrician, assuming that his practice also encompasses adolescence.

The important question which must be answered is this: If the tuberculin test is used routinely at about six-month intervals, will it be possible, by treating the tuberculous lesion early enough, to eliminate the tubercle bacillus? There are those who believe that the tuberculin test becomes positive only after necrosis, and it is this unanswered question which is our stimulus to continue study of this problem.

Dr. Robert B. Lawson, Miami, Fla.: One question that hasn't been discussed very much is the matter of dosage. This dosage of 4 to 6 mg. of isoniazid per kilogram is smaller than certain other centers have used. Miliary tuberculosis that developed in one case cleared up on the addition of aminosalicylic acid and increasing the dosage of isoniazid to 10 mg. per kilogram per day. I am wondering if Dr. Blatman has any information on whether these same findings might be found if the routine dosage was more in the neighborhood of 7 to 10 mg. per kilogram per day.

Dr. Waldo E. Nelson, Philadelphia: Were any children or group of children who had no positive tuberculin reaction at any time studied by means of gastric washings?

Dr. Saul Blatman, New York: First of all, in answer to Dr. Stevenson, how many retests were done with old tuberculin and how many with PPD?

The protocol of the study calls for the use of PPD, and so the majority of the children were tested with PPD initially and then at 12 months. However, if they were negative, either to the second or third tests of intermediate PPD, we did then use old tuberculin, 1 mg.

Dr. Hodes remarked about the 5 mm. response to old tuberculin or PPD and whether this was a reliable test.

Again, the protocol calls for admission to the study of all children who show 5 mm. of erythema and induration. It is of interest that all children who had positive gastric tests and at the same time negative skin tests at no time showed more than 12 mm. of erythema and induration.

Dr. Lawson discussed the dosage of 4 to 6 mg. per kilogram of isoniazid.

I don't know whether the child who developed miliary tuberculosis would have developed it on a higher dosage initially. I think the thing that is interesting is his response to an increased dosage when it was raised to 10 mg. after he developed the complication. He responded very quickly; I believe more quickly than he might have had he been treated with placebo initially.

In answer to Dr. Nelson's question, whether there were any children who did not have positive intradermal tests studied by gastric washings—no, we had no such children in the study.

**Studies on Acquired Tolerance to Homografts, Heterografts, and Tumors.** Robert A. Good, Ph.D., M.D.; J. B. Aust, M.D.*; Carlos Martinez, M.D.*; Richard H. Egdahl, M.D.,* and Richard L. Varco, M.D., Ph.D.,* Minneapolis.

The definition by Billingham, Brent, and Medawar, in England, and Woodruff, in New Zealand, of a new immunological phenomenon referred to as acquired tolerance has opened broad new vistas for immunological research. Briefly defined, "acquired tolerance" is a state of immunological unresponsiveness induced when exposure to antigens occurs during the period of immunological immaturity. During the past one and one-half years we have carried out studies on the phenomenon of "acquired tolerance" to heterologous, homologous, and tumor tissue. In these studies, rats,

* By invitation.

rabbits, humans, and inbred strains of mice have been employed. Thus far the results obtained permit description of the following phenomena.

1. We have produced complete tolerance of skin by injection of viable spleen cells during fetal life in rats. These observations confirm the existence of the phenomenon of acquired tolerance as defined by the British workers.

2. We have produced partial acquired tolerance to ovarian homotransplants in mice by injection of viable spleen cells during fetal life. The tolerance produced was sufficient to permit, after castration of mature animals, survival of the transplant and endocrine function attributable to the ovarian transplant lasting for a period of approximately one month. No evidence of ovarian function was observed in nontolerant immunologically mature mice provided with ovarian transplants in a manner identical to that used in the tolerant recipient.

3. Partial tolerance to skin heterografts developed in rats and mice following injection of viable rabbit spleen cells during fetal life but not in rabbits injected with rat spleen cells at a comparable period of gestation. In these studies the development of circulation and rejection pattern of rabbit skin heterografts transplanted to the rat was demonstrated. When rat skin was transplanted to rabbits, circulation in the graft and initial take of the graft did not occur.

4. Homotransplantation of mouse mammary adenocarcinoma within the first few hours after normal birth was regularly successful between A and $C_3H$ strains of mice and vice versa. The majority of mice provided with these tumor homografts supported the foreign tumor, which grew progressively, metastasized, and ultimately destroyed the recipient mouse. The tumor growing in the foreign host retained its immunological identity, since it could be transplanted back into only the original donor strain and would not take and grow in immunologically normal members of the strain which had been made "tolerant" by the inoculation of tumor suspension within the first few hours of life. In other experiments strain differences in the capacity to develop acquired tolerance to tumor homografts was demonstrated.

5. Homotransplantation of mouse mammary adenocarcinoma was regularly successful in mature mice given injections of spleen cells from the prospective donor strain during the first few hours of life.

6. Heterotransplantation of mouse ($ZC_3H$) mammary adenocarcinoma to rats by the injection of tumor cells during the immediate neonatal period resulted in initial progressive growth of the mouse tumor followed by subsequent rejection of the tumor in 65% of the rats injected, progressive growth of the tumor to death in 13% of the rats, and failure to take the tumor in 22% of the rats.

7. When mice bearing homologous tumors previously transplanted in the neonatal period were placed, after weaning, in parabiosis with immunologically normal nontolerant mice of the isogenic strain, the tumor on the tolerant member of the pair did not regress. Instead, the normal parabiont became receptive of transplantable tumor from the same strain of mice from which the tumor was originally derived. It would appear from these observations that susceptibility to tumor homotransplantation may be transferred by means of the parabiotic linkage. The basis of this observation is not yet clear, but the data might be interpreted to indicate that an enhancing factor permitting the homotransplant to take in the immunologically normal parabiont, and probably produced by the tumor, is being transferred across the parabiotic linkage.

## Discussion

DR. ROBERT E. COOKE, Baltimore: Dr. Najjar was unable to be here, and so I am asking a question which he might ask if he were here. That is how Dr. Good might explain his findings in terms of the hypothesis that Najjar has put forth; namely, the development of an antibody to antibody itself, with blockade produced in that way.

DR. RUSTIN MCINTOSH, New York: I want to ask a very innocent question. Dr. Good obviously didn't have time to tell us many of the details which he must know about the nature of cells that he injects and the volume or amount of cells required to produce the phenomena, but we are already carrying out extensive natural experiments in using replacement transfusions in the neonatal period, and I wonder if there have been any attempts at homografts of skin later on in patients who previously had a replacement transfusion?

DR. HATTIE E. ALEXANDER, New York: I should like to ask Dr. Good what method he used for demonstration of antibody against the cells injected.

DR. ROBERT A. GOOD, Minneapolis: In this work, of course, Dr. Najjar's hypothesis and his very exciting experiments were considered. Thus far, we have not been able to carry out experiments which might provide really a link between what we are observing here, by taking advantage of the period of immunologically homologous strains, and Dr. Najjar's concept that antibody production is ultimately stopped by a succession of immunological reactions against antigen and antibody complex. Actually, experiments could be designed with simple protein antigen or enzyme antigen systems in which this question could be answered. Dr. Smith's data thus far indicate that, with simple protein antigens, the immunologically tolerant host does not recognize the antigen as being an antigen at all and thus deals with it as one of its own proteins. Dr. Smith and

I both, however, have considered the possibility that an incomplete antibody might be formed by the immunologically tolerant animals which has the capacity to prevent the chain of events postulated by Najjar, resulting in development of demonstrable antibodies.

As to the cells injected, actually we don't know the limitations of the requirement for this. The cells in most of these experiments which would produce the phenomena of acquired tolerance have been derived primarily from the spleen. These cells are taken from the spleen by a gentle teasing procedure and are gotten into the recipient host intraperitoneally or intravenously as quickly as possible.

The volume of cells that seems to be necessary is somewhere between 3,000,000 and 20,000,000 cells, and so it isn't really a large number, and some experiments indicate that the numbers can be rather small.

Provoked by this observation, we have taken these studies to humans, and in babies given exchange transfusion we have tried ultimate skin homotransplants. In these exchange transfusions we took great care to protect the integrity of the white blood cells. I might say in parenthesis that the British did actually induce tolerance in some of their animals by the injection of cells from the peripheral blood. Subsequent homotransplantation has been carried out with skin in these babies, and they appear to reject the homotransplant just as do normal persons.

In other experiments, working with babies with congenital adrenal hyperplasia, we have provided them, in the neonatal period, with white cells and bone marrow cells from their father. The babies were then grafted with father's skin when they were between 6 months and 1 year of age.

In some of these instances the homotransplants have remained on for prolonged periods, up to 65 days, but in no instance have we achieved what we consider to be the goal—namely, persistent and complete acquired tolerance in man. In several instances, for example, we have done reciprocal skin homotransplants between the baby and the father, and the baby's skin homograft on the father regularly is sloughed, between 14 and about 24 days after transplantation. To the contrary, these babies have retained the skin homotransplant more than 60 days. The slough of the baby's skin after transplantation to the father was always associated with a violent reaction and complete necrosis. In the case of the babies the transplant from the father gradually decreased in size, without significant inflammation or obvious necrosis. However, there is another variable here that we have not felt inclined to control, and that is the variable presented by the immunological immaturity of the baby. To avoid this drawback we have waited until the babies were 6, 8, and 9 months of age before carrying out these homotransplants. We have assumed that by this time they should have reached their immunological maturity. However, until someone studies the behavior of skin homotransplants in human infants, we cannot be sure whether the prolonged survival and gradual slough of the homotransplant is due to partial tolerance or to immaturity of the homograft-immunological response. The important point it seems to me is that thus far we have failed to produce complete tolerance of skin homotransplantation in man.

Now, we don't think that these observations eliminate the possibility of our being able to produce a transplant in man. Working with the animal systems it was extremely difficult for us to get the experiments going so that we could confirm the brilliant work of the British investigators. Working with a new preparation, i. e., human peripheral cells and bone marrow cells, in babies, it might require more delicate handling of the cells, might require larger numbers of the cells than those that we have thus far used. These babies have been given up to 1,600,000,000 viable cells; viability has been estimated by the Trypan blue technique.

With respect to the antibody methods used, we have not been working on the circulating antibody aspect, Dr. Alexander. I was quoting from the work of Gorer and Amos and some of the others who have demonstrated human agglutinating antibodies and cytotoxic antibodies in several in vitro and in vitro-in vivo systems.

In our own work we have not been directing our attention to measurement of a circulating antibody. As you are well aware, I am sure, there is some controversy in this field. The bulk of the evidence appears to indicate that it is a form of cellular immunity which is responsible for the homotransplantation rejection. Indeed, most investigators believe that the immunological reaction responsible is identical to the tuberculin reaction. I think that the most important argument against this as a complete hypothesis is the work that we have done with the agammaglobulinemic patients. We have shown that children with congenital agammaglobulinemia can tolerate skin homotransplants and keep them on for periods as long as three years. In two instances this has been the case. In other instances where the immunological phenomenon is subdued but not completely absent they have kept their homotransplants on longer periods of time than normal but slough has ultimately occurred. So we now think either that both kinds of immune responses are required for transplantation failure, that circulating antibody is required as a step in the reaction, and that the tuberculin phenomenon is another step in the reaction or that another mechanism dependent upon cells and perhaps somewhat different from that involved in the tuberculin

reaction is responsible for homotransplantation rejection.

**Epidemiologic Characteristics of Certain Phage Types of Staphylococci in a Newborn Nursery.** THOMAS E. SHAFFER, M.D.*; JACK N. BALDWIN, Ph.D.*; ROBERT F. SYLVESTER, M.D.*; MELVIN S. RHEINS, Ph.D.,* and WARREN E. WHEELER, M.D., Columbus, Ohio.

Investigations of epidemic staphylococcal disease in nurseries which have included bacteriophage typing as an epidemiologic tool have always incriminated a specific offending strain of Micrococcus (Staphylococcus) pyogenes. One epidemic strain in particular, phage Type 42B/47C/44A/52/80/81, has been involved in the majority of epidemics studied by this method (more than 40 epidemics throughout the world). This strain is particularly able to establish itself in the newborn (nasal membranes and skin) and to initiate infection even after long periods (up to two years) of asymptomatic carriage. Following the control of such an epidemic in our nursery, we placed the infants and personnel of one nursery under constant surveillance for two years and followed colonization by various strains of staphylococci. During this investigation other characteristics of particular strains of M. pyogenes were observed and methods of control of staphylococcal infections were evaluated.

Colonizing ability was apparently independent of pathogenicity. Under a strict regimen of hexachlorophene bathing, a single strain usually predominated in the infants and one or more permanent carriers were detected among the nursery personnel who had close prolonged contact with the infants. When a strain predominated in the infants, transient carriers of the strain were detected among the nursery personnel. Upon removal of the permanent carrier from the nursery, the strain disappeared abruptly from both the infant population and the transient carriers. Under such care staphylococcal disease appeared only at home after a few days or weeks in babies known to have pathogenic strains established in their noses before discharge. During periods of "dry" skin care, the incidence of nasal and skin colonization of infants increased markedly, apparently owing to infant-to-infant transmission of strains which had a high capacity to colonize. The logical extension of these findings is to make all staphylococcal disease in the first month of life reportable to public health officials in an attempt to locate any common nursery source of highly pathogenic staphylococci, since nursery personnel are usually unaware of staphylococcal disease arising in their discharged patients.

### Discussion

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: This paper is significant, for it demonstrates a useful tool for the study of this important infection in the newborn. It is similar epidemiologically to the phage method of tracing typhoid carriers.

When it comes to the matter of the infection itself, the problem is more complex, for the relative importance of the general and local factors of immunity is not yet really known. Some believe that coagulase is important and that anticoagulase in production has much to do with resistance. Recently we have become interested in the antihemagglutinin titer of the blood. I wonder if Dr. Wheeler would care to comment on this antibody and its possible relationship to staphylococcal immunity in infants.

### Discussion

DR. REGINALD WILSON, Vancouver, B. C., Canada: We have been studying this problem in our nurseries for six years and particularly in the last three years with the phage typing. Our results confirm the finding that the phage type V-81, as we call it, is predominant among the newborns. In fact, this strain has been the one most consistently recovered throughout the period of our study.

However, in our nurseries we have had brief periods when two other strains predominated.

I agree with Dr. Wheeler's suggestion that it would be desirable to make staphylococcal infection, discovered in the home after discharge, a reportable disease; however, I believe this would have a lot of practical difficulties. I wonder if one might not draw an analogy between the spread of milk-borne disease and dairy hygiene. Although the reporting of infections is an important factor here, I think that milk-borne infections were only controlled when universally high standards of dairy hygiene were instituted. I wonder if possibly the same thing does not apply to nursery care. We have found that the most vicious outbreaks of staphylococcal nursery infections are sometimes in the hospitals where nursery standards do not come under sufficient supervision or inspection.

DR. M. GROSSMAN, San Francisco: We have been studying this problem in our nursery for a couple of years. We have had two outbreaks in our nursery—the one which Dr. Shaffer labels the epidemic, or the V-81, is the one involved in all infections among full-term babies and their mothers. However, another strain, apparently of lesser virulence, has caused an outbreak limited to premature babies—one death was noted in a premature baby who additionally was shown to have cystic fibrosis of the pancreas.

I have two questions: How much trouble has this epidemic strain caused among siblings after the babies have gone home? Has surgical infec-

* By invitation.

tion in the hospital been caused by the same phage type? It has been in ours.

DR. RICHARD T. SMITH, Minneapolis: With the cooperation and help of the Columbus group we were successful in identifying the source and controlling of an epidemic outbreak of neonatal staphylococcal disease in Minneapolis. We are very grateful for their help.

With their phage typing facility we found a single carrier who was responsible for over 150 infant infections with the 42B strain, about 40% of which were considered serious and ranged from cellulitis to staphylococcal pneumonia.

Although we could prevent skin colonization and nursery infections by hexachlorophene bathing, as Dr. Wheeler has shown here, I wonder whether this also prevents nasal colonization? In spite of the hexachlorophene bathing, we still had babies who after going home developed infections and spread infections to their families, as long as the nurse found to be a permanent carrier of the epidemic strain remained in our nursery. Elimination of that carrier stopped the epidemic abruptly.

I wonder whether the Columbus group will continue to assist in typing staphylococci for epidemic investigations?

DR. ROBERT A. GOOD, Minneapolis: From the data presented, this problem is obviously one of world-wide importance. One thing which struck me from the data presented was the observation that these organisms are characterized by uniform susceptibility to erythromycin.

I wonder whether or not Dr. Wheeler has seen any of this "hot" strain, which is capable of such extensive colonization and pathogenicity, to be resistant to this particular antibiotic? What do you think of the routine utilization of erythromycin where an epidemic threatens as a means of preventing new cases and elimination of the disease from the nursery?

DR. ARTHUR H. PARMELEE, Pacific Palisades, Calif.: This problem of Staphylococcus infections in nurseries, of course, is not new. We are accustomed to it and have been for many years.

The thing that has interested me and the question I should like to ask Dr. Wheeler is whether or not the same clinical characteristics that we have been seeing in California with this identical phage type have been seen in all other places.

For example, we have thought about Staphylococcus skin infections in general as being rather superficial infections and seldom causing deep skin abscesses. In days gone by we did see mastitis in the newborn, salivary gland abscesses, and osteomyelitis of the maxilla with tooth bud infections, but they have been very rare in the last 15 years. Actually, for at least 15 or 20 years I have not seen a Staphylococcus osteomyelitis of the maxilla until just recently. We had two in one week at the Children's Hospital in Los Angeles. This and other rather devastating necrotizing lesions that invade the deep tissues is something that has come up very recently, at least in my experience, and something we have not seen for many years.

Another interesting thing is that I have not heard in any of the recent epidemics, except in one that was reported four or five years ago, of Ritter's disease being part of the epidemic picture.

DR. HATTIE E. ALEXANDER, New York: Three terms have been used which I should like to hear Dr. Wheeler define a little more in detail, "colonization," "epidemic," and "infection."

I think it is obvious that he is using the term "colonization" in order not to stick out his neck as to its true significance. It probably is a subclinical infection. It is clear, however, whatever its nature and however much the baby reacts to this colonization, that this is a very widespread phenomenon, which goes on, at least in our experience, just about all the time, and, from our studies, it is present in the majority of infants within 24 hours of delivery. In spite of this widespread colonization we have been without disease, staphylococcal disease, most of the time. We get little outbreaks. We have never had anything that could be called an epidemic.

I would like to know exactly how "epidemic" is being defined.

One reason why I raise this question is that the "dry" care of the skin is being incriminated as a possible cause for epidemics. We have been using it for many years, and we have not had reason to incriminate this method.

DR. WARREN E. WHEELER, Columbus, Ohio: Dr. Bradford, we have not yet studied the immune reactions in the infant. We do know that the so-called "hot," or epidemic, strain carries a full complement of virulence factors. Most of our specimens of this strain possess an extraordinarily high $\alpha$-hemolysin, in the neighborhood of 3500 units, which sets this strain somewhat apart from most pathogenic staphylococci.

Dr. Wilson, why should you report these epidemics? The answer to that question is that in many of the epidemics which we have learned about, and in our own, the last people to know that an epidemic was in progress were the people in charge of the nursery. In our University Hospital epidemic, we at Children's Hospital across town knew that an epidemic was in progress because of the discharged infants whom we saw in our outpatient department. The next group who knew was the obstetrical service, because of the mothers with breast abscesses, and the last people who knew were those in charge of the nursery. In most lying-in hospitals today, babies do not stay long enough to show their impetigo while still in the nursery; they get it when they go home.

As to Dr. Grossman's comment—may I just quote a little statistic which has been given me by Dr. Wentworth, of the Ohio Department of Health, who studied one of these "hot" strain epidemics in Lancaster, Ohio. Ten days after the epidemic, when he visited the babies in their homes, he still found a third of them colonized by the epidemic strain. In the subsequent six months 72% of the mothers of these babies had acquired colonization by this strain, and about 30% of the fathers and siblings had been colonized. Of these persons who had become colonized 72% of the siblings and about 40% of the mothers and fathers had developed staphylococcal lesions.

Dr. Smith, will the services continue? This is a big job, and we could not undertake to identify all the carriers in a nursery where an epidemic was in progress. However, Dr. Baldwin tells me that he can identify a strain or two from epidemic lesions and perhaps if one were to have a nurse with staphylococci in her nose with the same antibiotic-sensitivity patterns as the babies' lesions he could phage type such a person's strain. We would be glad to try to help any of you with this type of service.

Dr. Good, does erythromycin resistance develop when you use this drug in a nursery to prevent colonization? We have not seen the development of erythromycin resistance in this particular phage type under these conditions. You may find erythromycin-resistant organisms replacing the epidemic strain when you use erythromycin for prophylaxis, but so far we have not been aware that any of these strains have given rise to any continuation of the epidemic of impetigo.

Dr. Parmelee, yes, we have been very much impressed by the seriousness of clinical infections with this particular strain. We have seen osteomyelitis. We have seen seven infants in the last two years with staphylococcal pneumonia and empyema. Six of these cases were due to this particular strain. Two deaths occurred among the babies during the original epidemic.

Dr. Alexander, you asked about definition, which is a very good question. Some of the transient carriers display this organism in their nose only when in contact with the organism in the air or in the babies. We doubt whether these organisms really invade the tissues of these persons and persist because they multiply in the nasal tissues. Many of these persons yield only a small number of coagulase-positive staphylococci when their noses are cultured.

What we call permanent carriers are persons who carried the same strain week after week whether they were in contact with the nursery where the staphylococci were present or not. We cannot really vouch that their nasal mucosa was in a healthy state. We think that organisms in these persons implant themselves in the nose, reproduce vigorously, and live in a state of symbiosis with the person. We also think that there is a great difference between persons. We think along with the Army people that there are some persons who are "dangerous carriers" and some who are not. Maybe it is the persons who spit when they talk that are dangerous carriers; maybe it is the persons who are morose and do not say much in the nursery and never use their handkerchief who are not dangerous carriers.

The epidemic, as we defined it, was rather serious. Fifty per cent of the babies in our nursery acquired lesions, and thirty per cent of the mothers who nursed their babies acquired breast abscesses. I cannot guarantee you that all of the nurseries represented on our slide had epidemics of this degree of severity, but we were assured that they did represent epidemics and not simply a case or two of impetigo.

**Defects in the Biosynthesis of Thyroid Hormone in Congenital Goitrous Cretinism.** H. David Mosier, M.D.,* and Robert M. Blizzard, M.D.,* Baltimore. Introduced by Lawson Wilkins.

Congenital hypothyroidism in the United States is due principally to partial or complete absence of the thyroid gland or to a congenital defect in the hormonogenic mechanisms of the gland. In the latter group, a goiter will develop eventually if there is not adequate suppression of the pituitary thyroid-stimulating hormones with exogenous thyroid administration. Thus, cases of this group have been termed congenital goitrous cretinism, although the goiter may not develop for a number of years or may never develop if the case is adequately treated with thyroid. When cretinism is first diagnosed the goitrous group may be differentiated from the partially and completely athyrotic group by an avid uptake of radioactive iodine ($I^{131}$) by the gland and at times a by palpable thyroid gland.

In recent years chromatographic analyses of $I^{131}$-labeled compounds in the gland and body fluids have shown that defects in the steps of biosynthesis of hormone are responsible for the deficiency of thyroid hormone in the goitrous cretin. Stanbury and Hedge and LeLong et al. have demonstrated in certain cases that the defect may be an inability to organically bind iodide trapped by the gland. In these cases there is a prompt release of a large part of the trapped $I^{131}$ after oral administration of potassium thiocyanate. Another defect has been shown in other cases by Stanbury and McGirr and Hutchinson in which there is defective dehalogenation of free mono- and di-iodotyrosine by the gland and peripheral tissues.

We have studied two cases of goitrous cretinism by means of $I^{131}$ uptake studies and chromatographic

* By invitation.

analyses of the gland, plasma, and urine. Charts prepared from the data will be shown demonstrating that iodine was normally trapped by the gland, organically bound to tyrosine, and dehalogenated from free iodotyrosine and that only trace amounts of triiodothyronine and thyroxin were detectable in the thyroglobulin and plasma. The defect in these patients is probably at the final steps (or step) of thyroxin synthesis. The normal mechanism involved in this stage of thyroxin formation is not known but may be an enzymatic coupling of iodotyrosine groups in thyroglobulin to form iodothyronine. The congenital defects in our patients might be due to an abnormality in the hypothetical coupling enzyme or a steric abnormality in the structure of thyroglobulin.

Studies of this type may cast some light on the normal mechanisms in the biosynthesis of thyroid hormone.

### Discussion

DR. ANGELO M. DIGEORGE, Philadelphia: I should like to know how soon after the ingestion of the iodine the potassium thiocyanate was administered and the level of uptake. If I understood correctly, the uptake was in the vicinity of 5%; I would be interested in knowing how much this fell.

Many of the goitrous cretins have a very rapid uptake during the first few hours after the administration of radioactive iodine. This, however, will spontaneously fall, presumably owing to the rapid turnover of the iodine. As Dr. Blizzard has demonstrated, this period is a very poor time to administer the potassium thiocyanate. If one is trying to demonstrate the "dumping" effect, one should wait until the level of radioactive iodine in the thyroid has stabilized, usually sometime after 12 hours or, better, after 24 hours.

These goitrous cretins are extremely important. Since they demonstrate inborn errors of metabolism, a tremendous amount of light is being shed on the normal pathways of synthesis, and possibly of release, of thyroid hormones by study of such patients.

Last year I presented a paper concerning a child who was goitrous and mildly hypothyroid. She had an elevated $I^{131}$ uptake and an elevated level of protein-bound iodine. Only 50% of the circulating radioactive iodine was butanol-extractable, meaning that only 50% of the total circulating radioactive iodine could be accounted for by the thyronines and tyrosines.

We have since studied another infant with the same defect, a one-year-old hypothyroid infant without a goiter who had a 35% uptake of radioactive iodine and a low PBI. Dr. Stanbury has studied two siblings with what appears to be the same type of defect. The nature of the circulating material in these patients is not known. I am sure as times goes on we will find more and more specific types of defects, depending on the total number of steps in the synthesis of the thyroid hormones.

DR. W. A. REILLY, San Francisco: I wish to commend the Hopkins group for these ingenious studies; such are slowly advancing the solution of this complex problem—goitrous hypothyroidism with its possible multiple enzymes.

We have studied these cases by radiochromatogram (autoradiogram) since 1953, and we, too, find these components, including unknowns, in the radiochromatograms.

[Slide] This is a composite. The three autoradiograms on the left are from one patient at 24, 88, and 108 hours after she was given a sizeable dose of $I^{131}$. We see that there is some thyroxin in the blood stream at 24 hours and that there is a good deal of iodide; at 88 hours, for the first time, we can detect in her blood stream the mono- and/or di-iodotyrosine, and an unknown at RF 2, the lower part. At 108 hours all that remains is mainly whatever thyroxin she manufacturers, and unknown. This girl, then, releases mono- and/or di-iodotyrosine, and these are broken down ultimately and iodide goes out in the urine. We have also found mono- and/or di-iodotyrosine in her urine.

The one on the far right is from a second patient, 24 hours after a big tracer dose of $I^{131}$, and shows thyroxin, mono- and/or di-iodotyrosine, an unknown RF 2, and iodide.

Those who wish to try such autoradiograms should use the butanol-dioxane-ammonia solvent. It separates the lines better. One can more accurately distinguish the lines that I have called mono- and/or di-iodotyrosine.

We are finding these same components, mono- and/or di-iodotyrosine, and the unknowns, in urine, in stool, and in saliva; we are trying to identify the unknowns. This is a complex problem, as Dr. Blizzard mentioned; one must give a large tracer dose. This is not ordinarily justifiable unless the whole thyroid gland is to be removed.

We find increased turn-over rates and decreased effective half-life of activity over the gland in this condition. This is a three- or four-day half-life versus the normal of six or eight days. We think that there is a greatly increased storage of organified iodinated compounds in the body. We cannot locate the storage area.

DR. ROBERT M. BLIZZARD, Baltimore: In response to Dr. DiGeorge, I am sorry that the slides could not be seen from the back of the room.

In the first patient the potassium thiocyanate was given at eight hours initially, and the uptake was 25% in that patient. She dumped 80% of the

iodine in the next few hours. This was artifact, of course.

I would like to comment on elevated PBI. Elevated PBI can occur in a hypothyroid patient, as Dr. DiGeorge has commented. An elevated PBI can occur as a result of a thyroglobulin-like substance being released into the circulation. It also can occur if mono- or di-iodotyrosine are liberated into the circulation. The latter is true if an alkaline precipitation of the PBI is performed, and most laboratories do use this method. To more adequately evaluate thyroid status we recommend that determination of the butanol-extractable iodine be used.

**Stable Iodine Measurement in Plasma, Thyroid, and Urine in Hypothyroidism, Colloid Goiter, and Hyperthyroidism.** W. A. REILLY, M.D.; K. G. SCOTT, Ph.D.,* and J. N. CASTLE, A.B.,* San Francisco.

The purpose of this study was to measure by a new method the changes of diffusible iodine in several thyroid states and from such changes to note where iodine deficiency or excess might exist. Stable iodine ($I^{127}$) was measured in urine along with a tracer dose of $I^{131}$; both isotopes were separated from urine by passage through a AgCl column. The resultant AgI was converted to $I^-$ and measured spectrophotometrically. The total iodide recovered was calculated by counting the $I^{131}$ with a scintillation counter. The method measures only that iodide which is exchangeable—inorganic iodide. From these data the quantities of $I^{127}$ in plasma and that going into the thyroid gland and into the extrathyroidal pool and space were calculated. This new method is simpler and possibly more reliable than the Barker measurement.

Comparisons with normals (nine children) follow. Plasma levels of patients with acquired hypothyroidism (five patients) and patients with goitrous hypothyroidism (four patients) were decreased, the latter significantly so. Plasma levels of patients with simple goiter (five patients) were the same as those of normals. Thyroid uptakes were lower in cases of colloid goiter and higher in goitrous hypothyroidism, but not significantly. The $I^{127}$ uptake in acquired hypothyroidism was significantly decreased ($P<0.02$). Urinary excretion rates were decreased in acquired and goitrous hypothyroidism, but not significantly so. The excretion in patients with simple goiter was the same as in normal persons. The extrathyroidal iodide pool and space were decreased in simple goiter and in acquired and goitrous hypothyroidism. Hyperthyroid patients (three patients) had plasma levels of normals; at the other parameters the results were the reverse of those in patients with acquired hypothyroidism.

The decreases of stable iodide, when the intake is supposedly adequate in our area (San Francisco), do not have a logical explanation. Absorption was probably not impaired, for fecal excretion was normal in the several so measured and urine excretion was not disturbed. In hyperthyroid patients the increases in pool and of space may be a conservation, for the excretion is decreased.

*Summary.*—Some iodine poverty seems to exist in plasma, thyroid uptake, extrathyroidal pool and space, and urine of hypothyroid patients without and with goiter, except that in the latter there is a greater than normal $I^{127}$ uptake by the thyroid. In simple (colloid) goiter the amounts of $I^{127}$ are normal in plasma and urine but there seems to be iodine poverty in thyroid uptake and extrathyroidal pool and space. In hyperthyroidism increases in pool and of space may be a conservation by the body.

### Discussion

DR. W. A. REILLY: We were measuring by this procedure only the amount of inorganic iodide which went into the glands; we were not measuring the total amount which exists in the gland. This requires the weight of the gland—practically an ablation, which, of course, is an impossibility with children.

Marine and his group were able to do that on experimental animals between 1909 and 1915. They found that the amount of iodide in the normal thyroid gland and the colloid goitrous gland was about equal; the amount in the hyperthyroid gland was less than normal, depending upon the degree of hyperplasia. Such measurements were also done on human glands. I thought this explanation might help some of the audience who may have been confused by the measurement of iodide; this was only that amount going into the gland and not the total amount existing in the gland.

**Indications for Oxygen Therapy in Small Premature Infants.** HERBERT C. MILLER, M.D.; FRANKLIN C. BEHRLE, M.D.,* and NED W. SMULL, M.D.,* Kansas City, Kan.

The survival of small premature infants does not depend on the routine use of continuous oxygen therapy. In a group of more than 60 infants with birth weights from 1001 to 1750 gm. born consecutively at the University of Kansas Medical Center, 26 survived without benefit of oxygen therapy; 9 of these infants weighed less than 1501 gm. at birth; the smallest had a birth weight of 1170 gm. Survival without benefit of oxygen therapy depended on unimpaired respiratory function and not on the infant's birth weight. Respiratory function in these small premature

* By invitation.

infants was evaluated routinely by observing the trend of their respiratory rates and in some infants by serial measurements of tidal and minute volumes, pH, $pCO_2$, and $O_2$ saturation of the blood.

If the respiratory rate did not increase significantly following birth, and severe apnea and bradypnea were not observed, oxygen therapy was not required and hebdomedal deaths did not occur. $O_2$ saturation of the blood was always above 90%. The pH was either normal or, if low, returned to normal within three or four hours of birth. Resting tidal volumes tended to be higher and minute volumes lower than among infants with respiratory insufficiency.

If the respiratory rate increased significantly after birth, and periods of severe apnea and dyspnea were frequent occurrences, oxygen therapy was required; it was used in 70% of the infants, and half of those receiving oxygen therapy died during the first week. Failure to initiate spontaneous sustained respirations within two minutes of birth (severe initial apnea) or to attain a respiratory rate of 40 or more per minute during the first hour (severe initial bradypnea) were universally associated with a subsequent significant increase in respiratory rates; each was attended by a fatality rate of 50%, and if they occurred together in the same infant the fatality rate was 100%. $O_2$ saturation was not infrequently below 90% during the first day or two following birth. The pH of the blood also tended to be low during the first two days. Minute volumes were high and tidal volumes tended to be low during the period of acute respiratory insufficiency.

It is concluded that oxygen therapy is not necessary for the survival of small premature infants provided that they (1) are free of cyanosis within a few minutes of birth, (2) initiate spontaneous sustained respirations within two minutes of birth, (3) attain a respiratory rate of 40 or more per minute during the first hour, and (4) do not have a significant increase in their respiratory rates after the first hour.

### Discussion

DR. ETHEL C. DUNHAM, Cambridge, Mass.: I should like to ask whether obstetric anesthesia played a role in causing periods of apnea in any of these infants.

DR. ROBERT A. GOOD, Minneapolis: I presume that your definition of the need for oxygen therapy is the development in these patients of hypoxia, but I think that this should be clearly pointed out. I, for one, would like to know whether or not in any of your data you have evidence that the patients in Group 3, who you think need oxygen therapy, have received any demonstrable benefit from this treatment. It seems to me that it would be reasonable, without further evidence, to interpret the data presented as indicating that a serious hazard derives from defining these patients as having a need for oxygen therapy. Maybe what is necessary is exactly the opposite approach—namely, withholding oxygen rather than giving it when the "need" is apparent.

DR. WILLIAM A. SILVERMAN, New York: At what environmental temperature were these observations of respiratory rate made? May I also ask about the incidence of exceptions in Group 3. We have observed infants at Babies Hospital with respiratory distress as evidenced by thoracic retractions who do not go on to exhibit an acceleration of respiratory rate. Although these infants are, in our experience, in the minority, they are missed by the rate-pattern screen.

DR. RALPH V. PLATOU, New Orleans: I can not resist remarking on the exceptions, and I should like to ask the authors the frequency of exceptions they have observed in each of the three classes.

In our own unit, observations have been made on respiratory rate and a number of other features, to characterize the condition of the premature infant, and when it comes to the individual baby we are convinced that there is no single measure or combination of these which will yet permit an accurate prognosis.

DR. JOHN M. CRAIG, Boston: I should like to ask if the authors have any data on the $CO_2$ alveolar tensions, because it might be possible that the $CO_2$ tensions were getting very low in the presence of the comparatively high oxygen.

DR. HARRY H. GORDON, Baltimore: I should like to ask whether the authors know if the administration of oxygen during the first hour can keep a baby who is a candidate for Group 3 from getting into difficulty.

DR. STEWART H. CLIFFORD, Brookline, Mass.: I should like to ask the authors to clarify a practical point for me. Since the subject of the paper is "Indications for Oxygen Therapy in Small Premature Infants" and since this is a problem that must be decided in each of these small infants, I am not convinced that on the basis of the material presented I would know what the authors' indications for therapy were. I would be more inclined to accept the conclusion if it had been possible to give us the results of a controlled study. The authors apparently have proceeded on the assumption that a certain group of small premature babies actually do need oxygen, but there have been no data submitted that have substantiated this.

DR. PAUL M. TAYLOR, Pittsburgh: I wonder if the authors have any indication from the maternal history as to which babies may get into

trouble; specifically whether the fetal heart rate was followed during the mother's labor and delivery.

I should also like to ask if the infant's pulse rate was followed during the period of observation.

DR. ARTHUR H. PARMELEE JR., Pacific Palisades, Calif.: I think it should be pointed out that a group in Sweden have taken a different tack. Dr. Goosta Rooth feels that the premature infants are operating at a low oxygen tension before birth; therefore he places them in 15% oxygen. His comment to me was that he had done this with 20 babies and they had done very well. I wonder if these investigators would comment on this.

DR. EDWARD B. SHAW, San Francisco: I should like to inquire whether there is any place in these studies for the baby that has initial tachypnea—rates of 60, 80, or more right at the start. Or are these simply babies whose rates are initially slow but rise so rapidly that you have not detected the early slow rate.

DR. HERBERT C. MILLER JR., Kansas City, Kan.: I think perhaps I can answer the questions of Drs. Silverman and Platou regarding the exceptions to the method of classification we have used. I do not believe the method of classification is 100% perfect. The method is at present based on certain arbitrary definitions, the main feature of which is a comparison of the average respiratory rate during the first hour after birth with the subsequent trend of the respiratory rate. I think the exceptions we run into amount to perhaps 4 or 5 infants out of 100, which makes it a pretty good biological method.

I think the important part of the classification consists in getting respiratory rates beginning at birth. We hope to get at least four readings the first hour after birth. In some of the smaller infants in Group 3, particularly those weighing under 1500 gm., the respiratory rates will average less than 30 a minute during the first hour; if the respiratory rates in such infants increase to 45 or 50 per minute after the first hour, this would be considered a significant increase; without knowledge of the trend of the respiratory rates during the first hour, a rate of 45 or 50 per minute after the first hour could be construed as normal. It is also helpful in doubtful cases to have readings made every hour instead of every two hours during the first two days.

DR. NED W. SMULL: In answer to Dr. Shaw's question, I think the Group 2 infants fit this category very well. These infants have also been followed by serial measurement of tidal and minute volumes, and their tidal volumes are significantly higher than those of the Group 3 infants.

Dr. Dunham, I do not have the answer as to the influence of anesthesia on our respiratory grouping. This is a study that is under way at the present time.

Dr. Good, I certainly did not intend to give the impression that oxygen was harmful to the Group 3 infants. We use a Water's oximeter with an infant earpiece as the criterion for the oxygen need of the Group 3 infant. The way we tell whether oxygen is helping is by the use of the oximeter and the disappearance of cyanosis. Oxygen saturations of 90% or above in the Group 3 infant obviate further use of oxygen in most cases.

Dr. Silverman, the environmental temperature used in this study was around 85 to 90 F. We do not find very many exceptions to the categorization of the respiratory groups, if the respiratory rates are followed from the time the infant is born. I think that some difficulty in interpretation may arise if the rates are not counted often enough during the first 24 hours of life. Respiratory rates are counted every 1 to 2 hours for the first 24 hours of life, and while they will vary considerably from time to time in some instances, it becomes rather easy to establish a trend in the respiratory rate and to differentiate the Group 3 infant from the infants in Group 2 and Group 1.

I have no data relative to Dr. Craig's question regarding $CO_2$ alveolar tensions in the late periods. We have shown previously that the Group 3 infants have a low pH, a high $PCO_2$, and low oxygen saturations initially. These usually return to normal within the first two or three days of life.

We have not found that the administration of oxygen will make it difficult to distinguish a Group 1 or Group 2 infant from a Group 3 infant, in answer to Dr. Gordon's question.

Dr. Clifford's question as to the criteria used for administering oxygen to the infants in this series revolves around the utilization of the oximeter. Certainly cyanosis alone was used in some cases as a criterion for the use of oxygen, but in many instances where cyanosis was not obvious, and yet the oximeter showed saturations below 90%, oxygen therapy was instituted.

Dr. Taylor, the pulse rate was not followed serially in our present study, and I have no data relative to the maternal history at the present time.

We have not used 15% oxygen in the infants in this study, in answer to Dr. Parmelee's question.

**The Health of the Ex-Premature: A Field for Further Study:** JOHN A. JAMES, M.B.,* Dallas, Texas. Introduced by Edward L. Pratt, M.D.

Premature infants who survive the neonatal period show a high rate of mortality and morbidity during the early years of life. The mortality

* By invitation.

rate of Negro ex-prematures was over three times greater than that of full-term Negro infants in the community (24.1 per 1000 vs. 7.9 per 1000). Ex-premature infants accounted for one-third of all deaths among Negro infants from 1 to 12 months of age.

A total of 534 infants weighing less than 2500 gm. at birth were born in a Dallas hospital during 1954, and 463 survived the neonatal period. Their subsequent progress has been compared with that of 506 comparable full-term infants. Over 80% of both groups were Negroes. During the first two years of life 14 ex-prematures and 4 full-term infants are known to have died; 12 of the deaths among ex-prematures resulted from infections and other theoretically preventable conditions. The ex-premature group also showed a high rate of morbidity, one-quarter of them requiring hospitalization during the first two years of life. Respiratory tract infections and diarrhea, often complicated by anemia and malnutrition, were responsible for 60% of the hospital admissions, and accidents and poisoning accounted for a further 10%. Morbidity was highest in the babies with low birth weights. Data concerning the premature infant from other sources suggest that this experience is not confined to any particular geographical area or racial group.

The occurrence of preventable mortality and morbidity seems particularly unfortunate in view of the prolonged and specialized care afforded these infants during the neonatal period. Factors contributing to these poor results which demand further study include the supposed inefficiency of immune mechanisms in premature infants, socioeconomic difficulties, and failure to achieve adequate parent education and continuing medical supervision during the critical years of infancy. These topics form the basis of a study program currently being set up to investigate further the poor health record of ex-premature infants.

### Discussion

Dr. Walter R. Hepner Jr., Columbia, Mo.: I should like to ask the author whether correlation was made between oxygen administration in the neonatal period and later morbidity and/or mortality of these infants.

The reasons for the question are two. The first is our demonstration (*J. Lab. & Clin. Med.* 48:817, 1956) of severe ganglion-cell necrosis in mice made hyperoxemic at specific stages of development of the nervous system and the clinical correlation made by Bakker (*Acta pædiat.* 43:529-542, 1954) between oxygen therapy in the neonatal period of humans and a high incidence of histologically similar central nervous system damage at necropsy.

Second, it has long been axiomatic that infants with central nervous system abnormalities (sometimes not recognized until later) commonly have a high morbidity from infections. This abnormally high morbidity and mortality was reported along with central nervous system abnormalities in about one-third of infants with retrolental fibroplasia studied by Hepner, Krause, and Nardin (Pediatrics 6:771-782, 1950) and was confirmed by several British investigators. Since we now know that hyperoxemia can produce retrolental fibroplasia with and without central nervous system damage and that either ocular or brain lesions are found in animals exposed to hyperoxemia at different and specific stages of development, it seems likely that some infants treated with oxygen may have central nervous system damage without evidence of ocular damage.

For the foregoing reasons, correlation of oxygen therapy with late morbidity and mortality might seem more than an idle statistical exercise, not only in this excellent work just reported but in other such studies as well.

Dr. Samuel Karelitz, Long Island, N. Y.: In view of our own experience that the premature infant frequently manifests evidence of infection shortly after discharge from the hospital, I wonder whether any correlation has been made with the bacteria found in these infections and what might have been present in the nurseries.

Dr. Arild E. Hansen, Galveston, Texas: I should just like to know what program is being carried on to educate the physicians in the community to see to it that these things are being followed up.

Dr. Charles W. McKean, San Francisco: I noticed with interest that there was a very relatively low incidence of congenital malformation noted in this group as compared with the full-term children. I wonder how many autopsies have been done to establish the cause of death of the youngsters in this premature group.

Dr. Julius B. Richmond, Syracuse, N. Y.: I wonder if there was any correlation made with a number of siblings in the family. I think this might bear some specific relationship to the occurrence of infection in these groups and may also be related to the matter of prematurity.

Dr. Andrew Sass-Kortsak, Toronto: I think this paper was a very clear demonstration of the fact that infections have a higher incidence in premature babies. It may be of interest to correlate the findings of the authors with a study of γ-globulin levels made by us a few years ago. In this study we determined γ-globulin levels in premature babies at the time of birth and compared these with the levels of the mothers at the time of birth. Serum γ-globulin levels were also determined in the prematures in the first few months

of life. We found that the smaller the premature the lower were the γ-globulin levels compared with those of the mothers. In small prematures the levels of γ-globulin may be only 40% to 50% of the mother's at the time of birth. This should mean, and Dr. Osborne and his group have demonstrated this, that antibody levels in the premature could also be only 40%-50% that of the mothers. Following up the changes in γ-globulin levels after birth in the prematures, we found that the well-known drop is occurring in these babies at the same rate as it does in normal infants. Therefore, one has to conclude that premature babies have much lower antibody levels, generally speaking, than full-term infants. I do not want to suggest that this may be the only mechanism responsible for increased incidence of infection in prematurely born babies, but I wonder whether the authors are contemplating the use of γ-globulin in prematures to prevent infections.

DR. HARRY MEDOVY, Winnipeg, Man.: I wonder whether the author has any figures on the incidence of kernicterus in this group, not due to blood-group incompatability.

DR. HANS G. KEITEL, Philadelphia: I wonder whether the authors made notes on the pattern of the mothers' behavior while they were in the hospital, during either the obstetrical or the post-obstetrical period, to see whether the mothers of the babies who had many infections differed from those who did not have many infections or other difficulties. It seems that accidents and poisonings occurred at a rather high rate in the babies with infections.

Would it be justifiable to institute a large expensive program for all mothers of premature infants when only 2% of the premature babies die? This is admittedly a high percentage but certainly a small proportion of the babies.

JOHN A. JAMES, M.B., Dallas: In answer to Dr. Hupner first, our indications for oxygen therapy follow the lines suggested by the previous speaker. We tend not to use it a great deal. We have not made any attempt to correlate the incidence of central nervous system damage or respiratory infections with the administration of oxygen in the nursery.

To Dr. Karelitz, we have not correlated the types of organisms found in the nursery with those found in the sick infants subsequent to discharge. This is clearly something that we ought to do.

To Dr. Hansen, we are attempting to bring more practicing pediatricians into the premature and newborn nurseries for teaching and service assignments, and we hope that this will further the interest of practitioners in the premature infant and his problems.

To Dr. King, the incidence of congenital malformation appears very low, but I believe this may be related to the small size of the sample. Autopsies were obtained in only about 50% of those babies who died, and so there may well have been other anomalies which were undiagnosed.

To Dr. Richmond, we did not complete the incidence of prematurity and the morbidity records with the number of siblings. In a previous study from England, this factor was taken into consideration but appeared to affect the over-all results very little.

To Dr. Medovy, we did not find any kernicterus in this particular group.

To Dr. Sass-Kortsak, I believe that γ-globulin has been given to premature infants in an attempt to prevent infections, but without any striking results. We did not measure γ-globulin levels in this group.

To Dr. Keitel, in our part of the country accidental poisoning is very common, and so an incidence of 10% may be not unreasonable. It may be apparently high because of the small size of the sample. We have not had the opportunity to look into the causes underlying this high incidence so far.

**Metabolic Studies of Infants Fed Pasteurized and Fresh Human Milk.** SAMUEL J. FOMON, M.D.,* and CHARLES D. MAY, M.D., Iowa City.

Data are presented concerning six normal infants, five boys and one girl, fed human milk by bottle during all or part of the first six months of life. A total of approximately 30 months of observation of the six infants and data from 57 metabolic balance periods are included.

Human milk was fed ad libitum by bottle, and supplementary vitamins A, C, and D, but no other foods or accessory food substances were given. The metabolism ward was maintained at relatively constant conditions of temperature and humidity to minimize daily fluctuations in the loss of nitrogen through the skin. A three-day balance period was carried out with each infant approximately every two weeks.

The infants consumed sufficient human milk to result in a mean intake of nitrogen of 351 mg. per kilogram per day at 1 month of age, gradually decreasing to 232 mg. per kilogram per day by the age of 6 months. All of the infants progressed along normal growth channels. At 1 month of age the mean retention of nitrogen was 170 mg. per kilogram per day, decreasing by 6 months of age to about 50 mg. per kilogram per day. These retentions of nitrogen are considerably less than those reported in the literature for a large number of infants receiving the greater amounts of protein provided by ad libitum ingestion of whole cow's milk and added carbohydrate.

* By invitation.

Because it was conceivable that the nutritional adequacy of the protein of the pooled human milk could be altered by the processing, consisting of pasteurization, freezing, storing, and eventual thawing, 24 metabolic periods were performed with seven infants receiving fresh human milk either directly from the breast or by bottle. The retentions of nitrogen of infants ingesting fresh human milk were the same as those of infants ingesting processed human milk. It was therefore concluded that the data from both groups could be interpreted as revealing the results of feeding normal infants human milk from the breast.

Although it is certainly possible to achieve greater retentions of nitrogen than that resulting from the ad libitum ingestion of human milk, it is by no means evident that this would be beneficial or even harmless. In endeavoring to state the requirements for protein when the source is cow's milk or other artificial feeding, it should be kept in mind that the maximal retention of nitrogen that can be forced on the individual may not be the same as the optimal amount for achieving an ideal state of nutrition. It would seem reasonable that, until more satisfactory criteria are available, the evaluation of substitutes for human milk should be based on growth and retentions of nitrogen at least equivalent to, but not necessarily greater than, those of infants fed human milk.

## Discussion

DR. WILLIAM M. WALLACE, Cleveland: I should like to ask Dr. Fomon if he has any ideas as to how he can account for the differences in body composition of the children fed on different levels of protein intake. If I remember his data correctly, he has nicely shown that the two groups of infants have the same growth increments and yet that the high-protein-fed infants retain greater quantities of nitrogen per unit of weight. Unless this indicates a differential rate of fat accumulation, the data are difficult to accept at face value.

It should be borne in mind that balance data involving algebraic computation with intake and output always involve a slightly positive error. No matter how meticulous the technique is, the subject never receives the calculated amount of intake; similarly, all of the excreta are never recovered. When large changes in balance are occurring, these small errors are insignificant. However, when very small net balances are being measured, as is the case here, these summated positive errors can become great. As the intake and output of a substance become larger and larger (as between human and cow's milk), while the balance must perforce remain about the same, the systematic positive error becomes greater and greater. If one were to go down to the ocean and set a course for Honolulu using a compass very slightly off, one could never expect to get there. One would more likely end up in Japan. I wonder if we can use balance methods for measuring such small changes during relatively small sample periods? Perhaps we would do better using methods for assessing total body fat, etc., and basing calculations on the known constancy of the mean body mass.

DR. HARRY H. GORDON, Baltimore: I wish to comment on this difference in composition of weight gain and am glad Dr. Wallace didn't attribute it to a difference in water content. In data that I published with Dr. Levine, we found no difference in relation of water balance to weight gain when we compared premature infants fed human milk of low protein and low electrolyte content with infants fed ordinary cow's milk mixtures in moderate amounts. Any difference in composition of weight gain was certainly not due to water.

DR. SAMUEL Z. LEVINE, New York: I might ask if other body constituents were determined, like hemoglobin and plasma proteins, as a measure of differences in body composition on these differential feedings.

DR. GILBERT B. FORBES, Rochester, N. Y.: I wonder if Dr. Fomon has calculated the results in terms of the weight gain of the infants, that is, nitrogen retained per kilogram of weight gained, and whether he has tried to correlate his figures with the scanty information available on actual body composition of newborn babies?

DR. DANIEL C. DARROW, Mission, Kan.: I hope you will not mind if I make some supplementary remarks. I don't know that my remarks really add anything to what Dr. Wallace said. I think a lot of people miss the point that the errors of balance techniques are negligible only when retentions are maximal or minimal. Consequently, the larger the retention or the larger the loss the more nearly you can believe the data. The difficulty in most balances is that the retentions or losses are a small part of the intake. Over a short period, the errors will not predict gross errors in body composition. However, over long periods, I am certain that when you begin to try to predict body composition, even with the most favorable circumstances, the errors can be very large. In the experiments under discussion, the errors seem to me insufficient to account for the predicted differences in body composition. In other words, it looks as though the breast-fed baby must have a different composition, but I think that in order to be sure we will have to actually devise methods for determining the body composition. The problems have been well discussed by Moore, who has done balances on surgical patients, and over short periods the balance technique seemed better, but over long periods, when big changes in body weight develop, we now have methods of determining body composition

that will predict these changes better than the balances.

DR. PHILIP L. CALCAGNO, Buffalo: During the past year we have had an opportunity to study a group of children to whom we offered a protein-free diet for the period of three weeks. The endogenous excretion of nitrogen in these patients ranged between 38 and 140 mg. of nitrogen per kilogram per day. These children were fed cow's milk. I think it might be of interest if one would feed children human milk and see what endogenous nitrogen excretion data can be obtained under this circumstance, with a protein-free diet. These endogenous nitrogen excretion levels with babies fed cow's milk and babies fed human milk could be compared.

DR. SAMUEL J. FOMON, Iowa City: I believe, as Dr. Darrow, that despite the errors inherent in the balance technique the retentions of nitrogen of infants fed human milk are certainly less than those of infants fed the usual formulas of whole cow's milk with added carbohydrate.

I should like to point out to Dr. Wallace that we did not say that babies fed human milk have the same growth as babies fed whole cow's milk with added carbohydrate. We only said that with six normal infants the growth curves fell in the normal range. We do not think that six babies are satisfactory for investigating a problem in which individual variation is such an important factor. This requires a large-scale study comparing babies fed human milk with babies fed cow's milk with the higher concentration of protein.

In answer to Dr. Levine, again, all we can say about the concentrations of hemoglobin and of total proteins is that they are within normal limits, and further evaluation of possible differences should be based on studies performed with many infants.

In answer to Dr. Forbes' question, the mean daily gain in weight was 42 gm. for each gram of nitrogen retained, and the standard deviation was ±12. This is considerably more gain in weight per gram of nitrogen retained than is reported in the literature in studies of infants fed whole cow's milk with added carbohydrate.

**Intake of Linoleic Acid in Relation to Serum Unsaturated Fatty Acids and Fat-Deficiency Symptoms in Infants.** ARILD E. HANSEN, M.D., Ph.D.; HILDA F. WIESE, Ph.D.*; DORIS J. D. ADAM, M.D.*; ARR NELL BOELSCHE, M.D.,* and MARY ELLEN HAGGARD, M.D.,* Galveston, Texas.

Although diets low in fat content have been used both therapeutically and experimentally, no concerted effort has been made to correlate the infant's dietary intake of linoleic acid with both the serum levels for *2*, *3*, and 4 double bond fatty acids and the clinical condition of the infant. It seemed indicated to pursue this problem because (1) mother's milk contains four to five times the amount of linoleic acid that is present in the usual cow's milk formula fed to infants and (*2*) the present-day tendency in some places is to stress the use of low-fat milk mixtures for the feeding of small infants. For this purpose one of the producers of infant foods (Baker Laboratories, Inc.) prepared for us five different milk mixtures having the same composition with respect to calories, protein, minerals, and vitamins but differing in the kind of fat and the amount of linoleic acid in the mixture. Of particular interest have been the two milk preparations which are very low in linoleic acid. In one of these mixtures carbohydrate was substituted isocalorically for all of the fat. In the other, the fat was composed of saturated fatty acids only. About 170 infants have been maintained for periods up to nine months on one of the five milk mixtures. Compared with the serum values in the infants who were given the milk mixtures having linoleic acid in the fat, the infants fed on the low-fat mixture, lacking linoleic acid, were found to have extremely low values for the *2* and 4 double bond fatty acids (linoleic and arachidonic) and high values for a *3* double bond fatty acid. The serum levels for these unsaturated fatty acids in infants receiving the milk containing saturated triglycerides (lacking linoleic acid) were similar to those in infants receiving no fat. In the two groups in which the milk preparation contained no linoleic acid it was necessary to change the feeding mixture in a large proportion of the infants because of the clinical findings associated with the skin and intestinal tract. Blood serum levels and the clinical symptoms were corrected by the administration of approximately 2% of the calories as linoleic or arachidonic acid as well as by shifting to a milk mixture containing unsaturated fatty acids. The serum level of di-, tri-, and tetraenoic acids in the infants receiving milk which contained varying amounts of linoleic acid correlated well with the intake of linoleic acid. This seems to have been the first extensive effort by prolonged feeding studies to evaluate the clinical and chemical responses of young infants to diets with and without linoleic acid. The preliminary conclusion may be drawn that the young human subject, just as is the situation in a variety of experimental animals, has a dietary need for the essential fatty acids. Determination of the *2*, *3*, and 4 double bond fatty acids of the serum is a good method of measurment of linoleic acid intake.

### Discussion

DR. HARRY H. GORDON, Baltimore: Last year Dr. Hansen presented some studies in which he related the total ad lib caloric intake of infants to the precentage of calories derived from fat.

* By invitation.

My recollection is that there was no difference between the caloric values of the diets taken by infants on full fat feedings (35% to 40% of the calories) and those fed "low"-fat diets, in which fat supplied 15% to 20% of the calories. On the other hand, the infants fed "low"-fat diets which were virtually devoid of fat show a significant increase in total caloric intake. I wonder whether in the observations he is now making Dr. Hansen has any studies on the intermediate fat intakes, which are used frequently in infant feeding, in contrast to the almost fat-free diets, which when used for only short periods of time.

Dr. John A. Anderson, Minneapolis: I am pleased to see after these many years, Dr. Hansen, the most convincing evidence of the effect of the deficiency and unsaturated fatty acids on the skin. I have watched this, as you know, practically since student days, and it seems that the evidence is slowly accumulating and looking more positive.

Two questions occur: We had a small child with chylous ascites due to a developmental anomaly in the nervous system, on a fat-free diet over a period of six or eight months. Dr. Holman at the Hormel Institute came in one day very excited because he reported the lowest values for diene and triene and the other unsaturated fatty acids in the blood of this patient after this low-fat diet. We failed to observe in this 3- to 4-year-old child over this period of time any real change of this nature in the skin. There was seborrhea of the scalp, but we found this was due to the fact that the mother did not scrub the head hard enough. For a moment we were excited, but the exudate was easily removed and this seborrheic activity disappeared.

Have you tried this diet in older children over a period of many months? Have you tried to give some of the water-soluble vitamins, particularly pyridoxine, to see whether an effect could be obtained similar to that which you have had with the administration of the unsaturated fatty acids?

Dr. Edward L. Pratt, Dallas, Texas: There is, of course, a great deal of local feeling in Texas, but, in spite of this, Dallas and Galveston have cooperated somewhat in these studies, and we may be able to throw some light on Dr. Gordon's question.

In Dallas we have studied premature infants fed these same mixtures that Dr. Hansen has illustrated. We noted the same sort of phenomenon as far as stools went on the very-low-fat mixture. In attempting to study all four mixtures and comparing them at random, we did not really come to any very satisfactory conclusions, because of the wide range of variability. Just using two mixtures, which both contained 42% of the calories as fat but which differed in the amount of unsaturated fat, we are able to show that the infants fed that mixture with the high unsaturated fatty acid content took about 3.6 Cal. to gain 1 gm. of body weight and that for those with almost no unsaturated fatty acid the average intake was about 5.4 Cal. per kilogram of body weight to gain 1 gm. This is a highly significant difference. It was consistent throughout the 11- to 20- and also 21- to 30-day periods; so there does seem to be some reason why infants fed these fat mixtures resembling the fatty acid content of breast milk do gain better at a lower caloric intake. Our studies, of course, were not designed to tell us why this happened.

Dr. Samuel Z. Levine, New York: Premature infants through the country, I think, are being fed low-fat cow's milk mixtures. It has been our experience that those on the low-fat cow's milk mixtures have fewer stools than those infants who are shifted to evaporated milk with twice the fat content. Practically all of them develop more frequent stools, which condition gradually subsides. It has been our experience, further, that skin lesions are not a characteristic phenomenon in these infants, even though they are fed on these low-fat mixtures for weeks or months. The gain in weight is equivalent on these mixtures to that of infants fed on higher-fat milk mixtures. I am ashamed to confess that I do not know what is the linoleic acid content of a 2% fat cow's milk mixture. I would be interested in knowing whether this low-fat feeding meets the criteria considered satisfactory by Dr. Hansen.

Dr. Daniel C. Darrow, Mission, Kan.: Did you culture the skins? In other words, did cultures reveal any susceptibility to certain infections?

Dr. Charles D. May, Iowa City: Knowing Dr. Hansen's interest in pyridoxine, I believe that he very likely has data concerning excretion of xanthurenic acid on the basis of tryptophan loading tests in this group of infants. We would all be interested to have him make reference to any such data.

Dr. Arild E. Hansen, Galveston, Texas: I think Dr. Pratt has answered Dr. Gordon's question in relation to caloric consumption. May I add that we have been asking our mothers to keep a record in the home of what the actual intake is, but I think that most of you are aware of the limited accuracy of data so gathered. We have considerable data, which are not yet reported, on 20 infants who were studied under hospital conditions.

Dr. Anderson reports that a child with chylous ascites had low value for the serum unsaturated fatty acids. This child had the equivalent of a low-fat diet, because fat was absorbed through the lacteals and accumulated in the peritoneal cavity; hence no fat reached the systemic circulation.

Perhaps Dr. Anderson remembers when we had a child in the hospital for 23 months who also had chylous ascites. We demonstrated extremely low iodine numbers of the serum fatty acids, but methods had not been developed at that time for the determination of the specific unsaturated fatty acids. Two observations stood out in relation to this child. When impetigo broke out in the infants' ward, the condition in this infant was much more difficult to clear up than that in the other children in the same ward. What is more, during the hot weather, when the infants developed prickly heat, the child with chylous ascites developed severe prickly heat which became a subacute dermatitis and remained until November; I remember that episode very well. So, again, there perhaps was something about the skin condition which may have been of significance in relation to the fat intake.

All of us have a great variation in what makes our skin be or feel normal, and I think we know very little about what the factors are. All we are able to maintain so far is that one factor which is concerned with the maintenance of healthy skin is perhaps linoleic acid.

Dr. Anderson also asked about older children having had similar types of studies. We feel that we have been fortunate to have this many infants to study. If Dr. Anderson remembers back a little further, when Dr. Brown was kind of an "old child" he was on the fat-free diet for six months. We found that metabolically and chemically this adult subject behaved exactly as experimental animals did under those same dietary conditions. Certainly we would like to study older children to find out more about the nutritional significance of linoleic acid.

Dr. Luzzati and I some years ago made a study of infants with cystic fibrosis of the pancreas and found their iodine numbers of the serum fatty acids to be in an far lower range than those of healthy infants. Had we had methods at that time for the determination of the specific unsaturated fatty acids, I do not doubt that they would have been low.

In regard to the pyridoxine given to these babies, no excess was prescribed. Again, I am glad Dr. Pratt answered the part of the question concerning premature infants. We have been enjoying extraordinarily fine relations in studying prematures. The advantage we have is that we live in a small town on a little island, and we have a good opportunity to follow the babies in a rather high percentage of cases. Dr. Pratt lives in a large city and has access to a large premature nursery. He and his co-workers have a more difficult time to track down the families after they have left the hospital; hence, he does not have as good an opportunity for the complete follow-up studies. We are collaborating in attempting to learn something about the feeding of prematures in relation to the specific fatty acids.

Dr. Levine mentioned the absence of skin lesions in the children in their studies. As I recall it, the milk mixtures which you fed contained about 15% of the calories as fat, and that would give you almost 0.5% of the calories as linoleic acid. We think it is rather interesting, in working with our dogs over some period of years, that Dr. Wiese and I found we had to give up to 15% of the calories as fat in order to prevent the skin evidences of fat deficiency. I am not surprised that the premature infants studied by you did not develop skin lesions.

The milk mixtures which we have used are much lower in total fat, and the linoleic acid content is way out of line in comparison with the milk preparations given to premature infants.

Dr. Darrow, we did not culture the skins of these babies.

Dr. May, we have made no attempt to carry on trypophan loading tests on these children.

**Chemical and Serological Studies on a Complex Carbohydrate Isolated from Patients with Fibrocystic Disease of the Pancreas.** CHARLES U. LOWE, M.D., and ERWIN NETER, M.D.,* Buffalo.

Prompted by the report that the duodenal contents of patients with fibrocystic disease of the pancreas (FCDP) contains a unique mucoprotein, we have attempted to isolate this substance from other sites in such patients, to examine the chemical composition of the material, and to prepare in rabbits antisera to the substances isolated.

A water-insoluble pellet was obtained from stool, sputum, bronchial mucus duodenal mucosa, and bile from patients with FCDP. The stool pellet could be fractionated into three components: carbohydrate I (CHO I), carbohydrate II (CHO II), and a nitrogen-rich precipitate (P). As isolated, none gave reactions for reducing sugars, but upon prolonged mild acid hydrolysis CHO I and II reacted with Symogi's reagent. Prior to hydrolysis both of these gave positive reactions for pentoses and $PO_4$, but absorption spectra suggested that these reactions might have been the result of nucleic acid contamination. The molecular weight of CHO I and II was over 1000.

CHO I, II, and P were obtained from various sources in good yield from patients with FCDP; small amounts were also obtained from stool but not from sputum of seven control subjects. Specific differences with respect to carbohydrate composition between CHO I from patients and from control subjects could not be demonstrated.

* By invitation.

CHO I, CHO II, and P were injected into foot pads of rabbits with Freund adjuvant. Specific precipitins appears in those animals receiving CHO I but not in animals injected with CHO II or P.

CHO I isolated from all patients with FCDP reacted with CHO I antiserum both homologous and heterologous to the patient. No reaction occurred with CHO II or P. CHO I isolated from three of seven controls also reacted with this antiserum. Absorption studies are now in progress to determine whether material obtained from patients with FCDP is different from that found in the control subjects.

Data indicated that CHO I was neither a blood-type-specific carbohydrate nor a Forssman type of sheep-cell antigen. CHO I could not be attached to red cells nor did it have propirodin-inactivating properties when examined in a chick embryo-Newcastle disease virus system.

These data not only suggest that a specific mucoprotein may be associated with the genetically controlled disease FCDP but indicate the possibility of serological diagnosis of the affection.

### Discussion

DR. PAUL GYORGY, Philadelphia: I should like to ask Dr. Lowe whether he has exchanged samples of his carbohydrate with Dr. Dische and whether it has been found identical with Dr. Dische's compound.

Secondly, whether he has hydrolyzed his carbohydrate, and whether he has been able to get a chromatogram and identify constituents with special reference to glucosamine in the hydrolyzed carbohydrate.

DR. ROBERT J. SLATER, Toronto: I should like to ask Dr. Lowe if his material bears any structural relationship, say, on the basis of immunological reactivity, to the trichloracetic acid-soluble mucoprotein which is found in serum and, furthermore, to the acid mucoprotein excreted in considerable quantities in the urine of patients with renal disease.

DR. CHARLES U. LOWE: The nature of the questions forces me to reveal considerable ignorance. We have done little more than we have presented. I wish we had more information to give you.

Dr. Gyorgy, you ask if the material is identical with that which Dr. Dische has isolated? You will have to ask him. He has had this material now for four months, and we are waiting to find out whether it is identical. I do not know. He indicated that he did not want to be hurried, and so we have not communicated with him.

As to the content of glucosamine, we have not determined the glucosamine, but the fact that 4% of the carbohydrate molecule is nitrogen suggests that it falls into the group of compounds in which the nitrogen is present in glucosamine.

Dr. Good, I am afraid that I am entirely unfamiliar with the method you mentioned.

DR. GOOD: It is the double-diffusion agar technique that I was suggesting.

DR. LOWE: No, we have not used it, and Dr. Neter, who is responsible for the serological data, unfortunately is not here, but he has been working on techniques to try to differentiate the normal material from that obtained from children with fibrocystic disease of the pancreas.

Dr. Slater, we have not done the experiment that you mentioned. All I can say is that we have obtained this material from patients who have no inflammatory disease, but that does not mean that it may not be identical with the TCA-insoluble material obtained from patients with inflammatory disease.

I might call to your attention the abstract of Drs. Dische, di Sant'Agnese, and Youlus in your program, in which these authors indicate that it is their opinion that the difference between the mucoprotein of normal patients and that of patients with fibrocystic disease of the pancreas is in the protein fraction, either quantitatively or structural—not in the carbohydrate fraction as they intimated a year ago. Certainly our results would have to be in keeping with that. We have not been able to find differences antigenically in the carbohydrate fraction.

**The Prognostic Implications of the Estimation of the Severity of Childhood Nephrosis.** WALLACE W. MCCRORY, M.D.*; DANIEL FLEISHER, M.D.,* and MILTON RAPOPORT, M.D., Philadelphia.

We have made observations that indicate that it may be possible to predict the ultimate outcome of childhood nephrosis relatively early in the course of the disease. The ability to estimate the gravity of disease shortly after onset is most desirable for the meaningful evaluation and orientation of treatment. In our experience, early prognostic judgments dependent upon the presence or absence of signs of nephritis are all too often erroneous.

The severity of glomerular damage in a group of 22 patients with nephrosis was assessed three years ago prior to the initiation of intensive steroid therapy. This was done as part of a study undertaken to clarify the mechanism of proteinuria in nephrosis and nephritis. An estimate of the amount of altered permeability of the glomerulus to albumin was obtained by measuring the albumin clearance and quantitative urinary protein loss. Glomerular filtration rate was simultaneously estimated by measuring the endogenous creatinine

* By invitation.

clearance. The patients were subsequently divided into three groups designated remission, improved, and unimproved, depending on their clinical and biochemical response to steroid therapy. We wish now to report the correlations between the amount of glomerular damage in the patients in these three groups prior to treatment and their subsequent response to intensive steroid therapy and their outcome three years later.

There were nine patients in the group in whom complete remission was promptly induced by steroid therapy. This group revealed the highest average value before treatment for glomerular filtration rate, 85% of normal; lowest rate for proteinuria, 2.7 gm. per day per square meter of surface area, and the least increase in glomerular permeability to albumin. The five patients unimproved by therapy were found to have the most marked evidences of glomerular damage before treatment. They had the lowest value for GFR, 55% normal; highest proteinuria, 6.1 gm. per day per square meter of surface area, and the greatest increase in glomerular permeability to albumin. Those patients who were improved but showed persistent proteinuria fell between these two extremes. Follow-up of these patients now reveals that the nine patients who responded with remission are still in remission. Those who were unimproved are now dead of renal failure. Of the group showing improvement but failing to show prompt remission, two are now in remission, five still have active disease, and one is dead of renal failure. Findings of nephritis were not regularly found in those patients subsequently doing poorly. It would thus appear that an ominous course is not solely dependent on the existence of signs of nephritis. These data suggest that the response to steroid therapy and the ultimate outcome in patients with nephrosis is related to the extent, severity, and reversibility of glomerular damage at the time of initiation of steroid therapy. Additional follow-up studies on other patients with nephrosis receiving intensive steroid therapy since 1954, supporting this prognostic hypothesis, will be presented.

## Discussion

Dr. Walter Heymann, I should like to say that Dr. McCrory's work is of obvious practical importance. I should like to ask two questions. In reference to the severity of proteinuria, a few years ago we reached the same conclusion as Dr. McCrory. Nephrotic children who never excreted more than 2 gm. of protein per day did well; children who excreted more than 6 gm. of protein per day over longer periods did poorly. That poses the question of whether our attitude to treat for proteinuria per se should be revised—at least concerning children with protein losses up to 2 gm. who will and do do well anyway, with or without steroid therapy. I should like to know what Dr. McCrory thinks about that.

The other question I should like to ask is whether the authors believe that the clearance of albumin is related to globulin clearance. We were able to confirm the old Blackman contention that the worse the globulinuria the more malignant the course of the disease. The connection between albumin clearance and excretion of globulin in the urine would be worth-while commenting on.

Dr. Henry L. Barnett, New York: I think a pattern is beginning to emerge in regard to the treatment of nephrosis with adrenal steroids and that this was indicated very nicely today by Dr. McCrory.

I should like to reemphasize the point that Dr. Heymann made. As we acquire more experience in the use of steroids, I think it becomes more and more important for us to find out the minimum amount of treatment required to produce the optimal effect in any disease. I think that the data presented by Dr. McCrory pertain to this general point. In addition, these data tend to substantiate the increasing impression that treatment with steroids very probably influences favorably the final outcome of this disease. Although I think we cannot be certain about this, I believe that it is hopeful. On the other hand, many of us are still seeing some patients who are diagnosed and treated early and yet the patients die of renal insufficiency. It would appear, therefore, that the adrenal steroids are not the ultimate answer to the treatment of nephrosis.

I should like to ask Dr. McCrory one question concerning the relationship between concentration of serum albumin and the ratio of the clearances of albumin and creatinine. There was a good correlation between these values and I wonder whether this is in disagreement with David Gitlin's observations that there is considerable variability in the rate of degradation of albumin in patients with nephrosis.

Dr. Malcolm A. Holliday, Pittsburgh: I should like to ask Dr. McCrory whether in the severe cases which rapidly progress to death he had any impression that cortisone therapy might have hastened this course? Most of his patients with renal failure appeared to die within three years from onset, and I do recall in the pretreatment era patients surviving much longer periods but having obvious renal failure.

Dr. Kurt Lange, New York: I think that the paper of Dr. McCrory is to be highly commended for bringing out the point that the cases which have initially the low clearance values and the severe proteinuria are those which require very intense treatment.

Dr. McCrory has stated that his cases had adequate therapy. I should like to ask him what he

considers to be adequate therapy. We have the feeling from our data that treatment with very large initial doses of steroids followed by maintenance therapy for at least one year leads to decidedly better results than treatment with steroids only when recurrences occur.

We now have a series of 51 cases observed for an average period of 36 months subsequent to the start of therapy. In this group, consisting of 39 children and 12 adults, there was only one death, a figure which is certainly very different from the data which Dr. McCrory presented. We treated them, however, much more intensely in the beginning and followed all cases, regardless of what the initial data showed, by maintenance therapy with large doses of cortisone for at least one year, as we have described previously.

I should like to ask Dr. McCrory whether he has the feeling that a case that initially during the first episode would be classified by him as "mild" may become much more severe when a recurrence occurs. This has been our experience, and so we like to avoid recurrences under all circumstances, for such patients may be quite refractory to steroid therapy in the second and third episodes.

Finally, I should like to ask Dr. McCrory whether he can confirm my experience that cases which did not have diuresis in several attempts with intramuscular corticotropin, cortisone, or prednisolone finally did have diuresis when corticotropin was given for 10 to 12 days by slow intravenous infusion. In my small experience with this method we were able to obtain diuresis in all cases which appeared to be refractory to steroid therapy.

DR. SAMUEL J. FOMON, Iowa City: Filtration rates are often normal or considerably above normal in patients with nephrosis, especially in those without other evidences of severe renal damage. I wonder whether the authors would care to comment on the mean creatinine clearance that was 85% of normal in the 11 patients in the prognostically favorable group.

DR. ROBERT E. COOKE, Baltimore: One short question—what is the relationship of the duration of the disease to glomerular permeability?

DR. WALLACE W. MCCRORY: I trust that the next two years will provide answers to some of these questions, because I cannot possibly answer them at the moment. I will try and touch on the points that the various speakers have made.

In response to Dr. Heymann's comments about the urinary A/G ratio, I would agree with the statements he made. In protein fraction clearance studies on children with nephrosis that we reported at these meetings some years ago, the relationship of the various globulin clearances to the albumin clearance did not provide a means of differentiating between patients with what I would now call a large leak and a patient with a small leak as long as there was massive proteinuria. Only in the presence of renal failure did the difference between the globulin and albumin clearances greatly decrease and did we find a definite low urinary A/G ratio. However, we found that by the time the low A/G ratio was found the fact that the patient had chronic renal disease was apparent by other means.

The questions centering around therapy can be answered most easily if I make some general comments. Regarding comments raised about the hazards of long-term steroid therapy, I could not agree more with what has already been said. I have not had time in this paper to give details of treatment. The important point we are trying to emphasize is that we have observed a significant drop in mortality rate only with intensive steroid therapy on indication. Thus, we feel that the hazard of persistent steroid therapy is warranted only by the hazard of a high mortality rate. If we consider persistent proteinuria as evidence of continued activity of renal disease, patients having persistent proteinuria have the probability of a fatal outcome. It is consequently our feeling that the condition of these patients warrants intensive steroid therapy, since their outlook without treatment is poor. I have been asked what we consider adequate treatment. We start intensive steroid therapy for every child for whom we have definite laboratory findings of nephrosis. We continue treatment until patients show diuresis and then watch for evidences of disappearing proteinuria. In those patients showing cessation of proteinuria, we continue treatment until serum albumin and erythrocyte sedimentation rates are normal or near normal. Steroid treatment is then discontinued, and such patients are then re-treated only if relapse occurs. In patients showing loss of edema but showing persistent proteinuria, we determine the maintenance hormone therapy required to maintain the edema-free state. We stop this therapy only when proteinuria becomes insignificant. By maintenance therapy, we mean high-dosage therapy for three to four consecutive days out of each week. Thus, you can see, we are giving adrenal therapy only on indication to patients showing signs of nephrosis such as persistent proteinuria and hypoalbuminemia. We stop therapy in patients in complete remission and in this manner avoid treating patients who have no evidence of activity of their disease. It is worth pointing out that hormone therapy is only one part of the general management of these patients, which must also consider diet, salt intake, and the close attention to prevention of intercurrent infection.

The comment about clearances by Dr. Fomon was a good one. The previously popularized supernormal clearances have apparently disappeared or are at least infrequent. As to patients with reduced

clearances who subsequently did well, there was one patient in the group who went into remission who had a glomerular filtration rate of only 50% of normal at the onset of treatment. The permeability index of the glomerular leak in that patient, however, was at 0.5, thus indicating a mild leak. The findings in this patient stress our point that there can be functional suppression in GFR. Thus, elevation of blood urea nitrogen early in the course of nephrosis may subsequently be found to be reversible. The fact that there is functional suppression in glomerular filtration rate will obviously not become apparent until the subsequent course of the patient indicates that improvement in renal function has occurred.

Dr. Holliday asks whether steroid treatment hastens death. We do not have a large group to judge from, but my general impression would be that the answer might be yes. In those patients receiving intensive treatment who had a fatal outcome, death appears to have occurred earlier than it would have with other forms of treatment. The only excuse for not stressing the hazards of steroid therapy is that we are trying to indicate that total deaths in patient groups observed for three years seem to justify intensive steroid therapy on indication if we are to improve the outcome of patients with this disease. I wish to thank all of the commentators for their thoughtful comments, and I trust that I have answered the main points raised.

**Antibody Response of the Very Young Infant to Poliomyelitis Vaccine.** RANDOLPH BATSON, M.D.*; AMOS CHRISTIE, M.D., and BERTHA MAZUR,* Nashville, Tenn.

Eighty infants were given three immunizing doses of poliomyelitis vaccine, each infant receiving the first injection at the age of 6 weeks or younger. The objectives were to determine the youngest age at which infants would respond antigenically to this vaccine and whether such response was equally favorable when poliomyelitis vaccine was mixed with other common vaccines and given as one injection. It was felt that if significant antibody responses were demonstrated in this age group the poliomyelitis vaccination program could be integrated into well-established well baby and immunization procedures.

Study Group I: Forty infants received 1 cc. of poliomyelitis vaccine at the ages of 6 weeks, 10 weeks, and 9½ months. When administered as a separate injection poliomyelitis vaccine was given in the right lower extremity and diphtheria, whooping cough, and tetanus vaccines were given in the left lower extremity. Study Group II: Forty infants were given poliomyelitis vaccine according to Study Group I schedule, the only exception being that the poliomyelitis vaccine was administered in the same syringe with diphtheria, whooping cough, and tetanus antigens and given in the right lower extremity.

Immediately preceding each vaccine injection 10 cc. of clotted blood was obtained from the internal jugular vein. Samples were also obtained two weeks and four months after the third (booster) injection. Standard neutralization tests for antibodies to poliomyelitis were performed on all sera. Significant antibody responses were observed in practically all infants in both groups.

Our conclusions are the following: 1. Immunization against poliomyelitis is effective when begun in infants 6 weeks of age. 2. Poliomyelitis vaccine is an effective immunizing agent when administered, according to our technique, in combination with other antigens. 3. There were no apparent hazards or adverse reactions associated with the above-described combination.

### Discussion

DR. MAURICIO MARTINS DA SILVA, Minneapolis: Since the objectives of this investigation, as stated in the abstract, were to determine the youngest age at which infants would respond antigenically to poliomyelitis vaccine, I believe that it would be of interest to mention here that for the past six months, in Minneapolis, we have also been working in this same direction, except that we have used, instead of the Salk vaccine, the living attenuated strains of Types 1, 2, and 3.

Our group includes, so far, 25 infants ranging in age from 4 days to 6 months, 14 of which were fed Type 1 virus under 2 weeks of age; 10 of these 14 were under 1 week of age. Our immunization program consists of feeding Type 1 on the day the baby goes home from the hospital, usually the fifth day, followed by Types 3 and 2 at three-week intervals. By this schedule we have been able to complete the immunization against all three types under 2 months of age; I might add that the infants in our study were born of mothers who received the Salk vaccine during pregnancy.

Now, how successful has this attempt been? Preliminary data on 14 infants, for whom antibody titers were available three weeks after completion of the immunization, indicate good to excellent antibody response to all three types. Intestinal multiplication of the virus, as demonstrated by positive stool cultures for Type 1, were found in 75% of our group, in spite of rather high levels of circulating placental antibodies to Type 1. To summarize, I should like to state that the oral administration of Types 1, 2, and 3 living attenuated poliomyelitis viruses to 25 infants has been remarkably symptomless; no clinical changes have been observed to date.

* By invitation.

I should like to ask Dr. Batson whether he has followed the antibody levels in his infants beyond the last blood specimen presented in his slides.

DR. HAROLD K. FABER, San Francisco: My congratulations to the authors of this excellent study of a problem important to every practicing pediatrician. Their results in humans gratifyingly confirm those of Kendrick and Brown in monkeys, disprove the assertion that poliomyelitis vaccine should not be mixed with triple antigen, and lead us to believe that in the very near future our routine immunization program will involve only three instead of six injections and correspondingly reduce the amount of psychic as well as of physical trauma to which our long-suffering patients are subjected. There is one aspect of the problem, however, which must be settled first and which I take the liberty of discussing: the interval between the second and third injections. The authors have used the long seven-month interval which, in the case of polio vaccine, has been insisted upon by the National Foundation and, in particular, by Dr. Salk, and has been so widely adopted by pediatricians as to have become almost a fixture in practice. This is some five to six months longer than is generally used in the case of DPT injections. Last October, in a letter to *Pediatrics*, I protested that the necessity of waiting seven months for the third shot of polio vaccine was very poorly documented, that there was sound reason to suppose that a much shorter interval would be sufficient, and that under the seven-month rule many children, particularly during the period of greatest risk, would be protected against the paralytic disease by only two immunizing doses, which have been shown to be considerably less effective than three. I strongly urged that further tests be made in human subjects of the antibody responses to third doses given at shorter intervals. Hoping that my letter might attract some attention, I was disappointed to find that the Committee on the Control of Infectious Disease of the American Academy of Pediatrics in its Red Book of 1957 continued to assert that the seven-month interval was necessary, as well as to say that triple antigen and polio vaccine should not be combined in the same injection.

It was therefore a matter of surprise as well as relief to find that Dr. Salk himself has recently made a study of the three-month interval, has demonstrated an excellent antibody response to all three types of virus in human subjects [Slide], and, in the last issue of the National Foundation for Infantile Paralysis information pamphlet, has modified his previously unvarying insistence on the seven-month or longer period in favor of a three-month interval, at least under certain circumstances.

While further studies of still shorter intervals might be desired, it seems to me that we are presently in a position to adopt with confidence a schedule of immunization with the four-way toxoid-vaccine based on intervals of approximately one month between first and second doses and three months between second and third doses. The same schedule would also be proper for polio vaccine given separately. Finally, I urge the Academy Committee on Control of Infectious Disease to reconsider its position at the earliest possible moment. Unless we change our schedules soon, a good many children and adults will go through the impending polio season with only the inadequate protection afforded by two doses of vaccine. If it is still desired, a fourth injection could still be given seven months or a year later. Indeed, with the enormous variability in antigenic potency of commercial polio vaccines discovered by Kelly and Dalldorf and by Shaughnessy et al., a booster dose at a year would appear to be a sensible precaution.

DR. C. HENRY KEMPE, Denver: I want to second Dr. Faber's comments, and I think that very likely the results Dr. Batson was able to get up to seven months would have been similar to those he would have gotten with a shorter interval between the second and third injections. But I think really the main significance of the study is to call attention to the fact that this immunization problem has, at least in the Armed Services, rapidly moved forward in the last few years, and that, while we have just gotten completely used to DPT, it seems strange that we are about to introduce a fourth antigen. The Armed Services in Canada and France, and at this time in the United States, are moving forward toward a 7- and 10-antigen vaccine. I think that in our short lifetimes we will all see very likely vaccination containing perhaps 20 antigens given in just this manner.

DR. WILLIAM C. DEAMER, San Francisco: I wonder whether as a by-product of this investigation, the authors have any information on the adequacy of the immune response when unintentionally the interval between the first and second doses has been considerably longer than the traditional six weeks.

DR. JOSEPH STOKES JR., Philadelphia: I think we all have good reason to be happy about the work that Dr. Batson has reported. I should like to ask him two questions: whether any cases occurred among these children or any epidemics occurred which might have enabled him to determine whether virus may actually have infected later the intestinal tract of the children who had been vaccinated and whether he has intended or expects to in the near future use attenuated virus in connection with these cases.

There is considerable evidence now accumulating that, whereas a naturally immune person who has had the disease under natural conditions is reinfected with difficulty in the intestinal tract, those

that have had the Salk vaccine are readily infected in the intestinal tract and then are apparently more apt to develop permanent immunity or at least antibodies that remain over a long period of time. It seems to me that since the antibodies do decrease rather rapidly in many cases following the Salk vaccine, the use of the attenuated virus in addition for a more permanent type of immunity is an important consideration.

DR. EDWARD B. SHAW, San Francisco: I should like to tell Dr. Kempe that I sample some of the mothers who come to me and they all assure me that their children have been immunized "to everything." I take it for granted that this includes diphtheria, tetanus, pertussis, and smallpox, but when I ask about typhoid and yellow fever they usually assure me that these have of course been done. It is useless to expect parents to keep careful track of immunization schedules, which illustrates the importance of careful record-keeping by the pediatrician.

The importance of this paper to me as a practitioner is the indication that poliomyelitis vaccine can be used effectively at a very early age. Accordingly, this is a very good procedure to initiate the course of immunization, because it produces less in the way of febrile response, systemic reactions, and the possibility of convulsive seizures than any of the other common immunization procedures. Once the first two injections are out of the way, other immunizations can be carried on at an appropriately early age. Although I have been a bit refractory to giving DPT at as early an age as 6 weeks, I am assured that it is good practice, and it is worth while to note that concurrent immunization can be carried on without adverse reaction.

I note with interest that the levels of antibody reported in this series—and please correct me, Dr. Batson, if I am mistaken—are somewhat lower than those reported in older children and adults with a similar series of injections. There is also the very strong implication that immunity induced in the very young persists more poorly than in older children. This is certainly true of smallpox vaccination, in which fairly early repetition will often provoke a second take in the child who has been vaccinated very early. Administration of poliomyelitis vaccine in the early months of life would appear to be worth while, but it is certainly suggested that the three doses might routinely be reinforced with a later fourth injection.

I have talked with Dr. Faber many times about the difficulty of arriving at a suitable interval for the third injection and that the arbitrary period of seven months is not too well documented. As a matter of fact, I originally thought somewhat cynically that this interval was arrived at as slightly in excess of the six-month life of the vaccine so as to make it impossible, in a period of short supply of the vaccine, for the physician to set aside a supply for those to whom he had given the first two injections.

There is great need for the physician to have a very definite program for this time interval in giving vaccine. Desirably, such official agencies as the Committee for the Control of Infectious Disease of the Academy should establish this definite time schedule, the limits of the interval at which a third injection should be given, and the necessity for fourth doses and perhaps later boosters. With the possibility that poliomyelitis vaccine is a relatively poor antigen and that some failures of protection may occasionally be encountered, it is worth while for the pediatrician to be able to state that he has followed an approved dosage schedule if these failures occur in his practice.

DR. HORACE L. HODES, New York: I should like to make two points: One is that we continue to talk about antibody titer as if we are talking about immunity. I should like to call attention to the fact that there are now on record four children who had no antibody who were exposed to polio. They developed viremia with polio virus but did not become ill at all, and so there are many other factors probably involved here.

The second point is this: We have seen falls in the titer of vaccinated children that have been very disturbing to us. These have occurred over a period of a few months with the titer having been at a fairly good level and then falling very rapidly, in line with what Dr. Stokes has said.

Now, finally, as to the members of the Committee that had to do with the vaccination program. The Academy Committee that was referred to by Dr. Faber made the recommendation which it did only because there was no other evidence to go on. We were not particularly happy with it, but we had to accept the seven-month interval, as I remember it, because that was what Dr. Salk said and there were not any other data to go on.

DR. J. C. PETERSON, Milwaukee: I should like to congratulate the authors on this simplification of the program of vaccination which will enable us to vaccinate children completely at an age when the psychic trauma is at a minimum.

I should also like to comment that it has been known for several years that children require a larger amount of antigen to achieve adequate antibody response in comparison with adults, and I think that it should be the understanding of all pediatricians that immunization programs are improvisations which are based on expediency to a large degree, in which we try to achieve a reasonably maximum result with a relatively minimum amount of antigen. It is obvious that a better response could be obtained if three injections were given instead of two or if more antigen could be

included in the amount in the original injections. Perhaps in the case of poliomyelitis the additional antigen would carry no additional reaction hazard, inasmuch as observed reactions have been relatively minimal.

In some unreported material concerning 500 children immunized with three injections of vaccine given at a total interval of six weeks, we have obtained a very superior antibody response in age groups ranging from 1 year to 14 years.

I think that the whole vaccination program is ready for rescrutiny, and this paper provides focal point for this reevaluation.

DR. EDWARD C. CURNEN JR., Chapel Hill, N. C.: Dr. Batson's paper is commendable and provides data needed by groups concerned with vaccination programs such as the Committee of the Academy of Pediatrics.

I should like to ask Dr. Batson to tell us how the lots of vaccine were selected for this study and whether different lots were compared for the capacity to induce antibody responses. I should also like to inquire whether any serologic tests were made to detect the development of antibody to monkey kidney protein constituents of the vaccine in those subjects who received the polio vaccine in the same injection with the DPT preparation. Under the circumstances, the latter might be expected to act as an adjuvant. This voices concern about the indiscriminate use in combination of currently available preparations of polio vaccine and DPT material, particularly if repeated "booster" injections are contemplated. Such use of this kind of mixture might result in the stimulation of antibodies against monkey kidney and thus be hazardous. It would seem advisable to inject polio vaccine and DPT separately until combinations of more refined polio vaccine and DPT can be appropriately tested and supplied commercially.

DR. RANDOLPH BATSON: Dr. da Silva, in regard to the antibody levels beyond 4 months of age, that is, beyond four months after the booster, there is an apparent fall in antibody levels about 11 to 12 months after the booster. These falls have been striking, and, although one would not like to be too dogmatic about it, they have been clearly in evidence in six to eight subjects that we have studied. I believe, Dr. Hodes, that that also answers a question that you asked and probably suspected also.

Dr. Faber, we have stuck to the seven-month interval prior to the booster dose simply because we wanted to be able to compare our results with other studies. We certainly agree that one is likely to get good antibody responses with a booster as early as three months. We have such studies under way at the present time.

We did observe a few patients, Dr. Deamer, who had their first two injections given at a much greater interval than six weeks, and we could see no difference in those. It seemed that the response to the two injections given at a longer interval was no better or no less.

Dr. Stokes, we have not had cases of intestinal infection that we could be certain of. However, in the older group of patients that we are now studying we do occasionally see unexplained tremendous increases in antibody responses, indicating that probably some intestinal infection occurred. We have thought of the possibility of observing the responses to an attenuated vaccine in a few patients at a later date. We will do this. Thank you for the suggestion.

Dr. Shaw asked a question concerning how early one can start giving polio vaccine. We have a group of patients in which the mothers are getting their first injection one month prior to their expected date of confinement, the newborn infant receiving the second injection and antibody studies at 24 hours of age. Nothing untoward has happened and no titers are available.

Dr. Shaw, in answer to your question, are our antibodies slightly lower than those reported in other studies?—I would say, in general, yes, they are. We feel that our antibodies are certainly at a protective level, but they are not at a level that is consistent with some previous reports in older persons.

Dr. Curnen, we made no selection of our vaccine whatsoever. At first we were hard put to get vaccine to start the study. This was two years ago. We actually used some vaccine that had probably diminished rather a lot in antigenicity because we wanted to use it before it expired. The rest of the vaccine was vaccine that is commercially available to all physicians. We did not make any tests for antibodies against the monkey protein constituents.

**ECHO Viruses Associated with Respiratory Disease in Children.** HENRY G. CRAMBLETT, M.D.*; LEON ROSEN, M.D.*; ROBERT H. PARROTT, M.D.*; JOSEPH A. BELL, M.D.*; ROBERT J. HUEBNER, M.D.,* and NORMAN B. MCCULLOUGH, M.D.,* Bethesda, Md. Introduced by AIMS C. MCGUINESS.

As part of a study designed to explore the role of certain prevalent viruses as causes of disease in children, a group of infants newly admitted to an orphanage in Washington, D. C., was studied in detail at the Clinical Center of the National Institutes of Health. The children varied in age from 5 to 14 months.

Eight patients were studied in whom there was a close association between the initial isolation of one of two types of ECHO virus and the onset of a mild clinical respiratory illness. In six (Group I) the virus was a newly recognized member of

* By invitation.

the ECHO group. For convenience, this agent will be referred to as JV-1 virus. In two (Group II) the virus was identified as ECHO Type 8 by reciprocal cross neutralization tests.

The major symptoms of these children included fever, coryza, and pharyngitis. The fever was of short duration, lasting two days or less in all of the patients. Rhinorrhea was an especially prominent symptom and lasted six to nine days. Other symptoms included vomiting, irritability, serous discharge from the eyes, and watery malodorous stools.

In only one patient was there slight increase in the size of the lymph nodes in the posterior cervical region. Moderate diffuse erythema of the anterior pillars of the fauces, of the tonsillar areas, and of the posterior pharynx was also present in all patients except one, in whom only erythema of the anterior pillars was noted. Mild congestion of the vessels of the palpebral conjunctiva was present in all. In six of the eight patients diffuse erythema of the eardrums occurred. In two of the infants purulent otitis media was observed as a complication. Three of the children were found to have scattered rhonchi upon examination of the lungs, but there were no localizing signs.

White blood cell counts varied from 6000 to 15,000, with preponderance of lymphocytes in most of the children. Five of the six patients in Group I had atpyical lymphocytes in their peripheral blood, whereas none were present in patients from Group II. The erythrocyte sedimentation rate was slightly to moderately elevated in all patients except one, whereas the C-reactive protein test was positive in only one patient. Five of the patients had abnormal chest x-ray findings, including increased bronchovascular markings, hilar adenopathy, and pneumonia. Serial antistreptolysin O titers, cold agglutinin titers, and heterophile determinations were negative. Skin tests for tuberculosis and histoplasmosis were negative. Nasal smears failed to reveal the presence of eosinophils. Bacterial cultures of the nose, throat, and stool did not reveal any etiological basis for the illnesses.

Both viruses were recovered from both throat and anal swabs. In relation to the illnesses, JV-1 virus was first isolated from the patients in the time from two days preceding to the day of onset of symptoms. The incubation period of this virus was found to be as short as 48 hours. JV-1 virus was excreted for as long as 26 days. All patients developed neutralizing antibodies against their homologous virus, and most developed complement-fixing antibodies.

Conversely, paired sera from the infants did not show a rising antibody titer against influenza viruses, adenoviruses, and certain Coxsackie A viruses.

## Discussion

Dr. Heinz F. Eichenwald, New York: I should like to ask several questions. I am wondering how many cases of completely inapparent infection with the JV-1 virus were noted in this population. How many infections were seen in older children and in children who were not institutionalized, and therefore subjected to multiple exposure in a large group?

I should also like to know if well children of various age groups not living in institutions have had antibody tests against this particular virus in order to determine what the incidence of this disease is among "normal" population groups.

The reason I ask these questions is because it has become apparent in the past year or two that some of these agents tend to cause disease only among persons closely crowded together and also that an agent which causes one type of disease among young children may cause an entirely different illness among older children and adults.

Dr. Robert E. Cooke, Baltimore: I should like to ask whether or not these sera were set up against the chimpanzee coryza virus. This virus was responsible this past year for a significant epidemic of respiratory tract disease in somewhat older children in Baltimore, accounting for 20% to 40% of our pneumonias in the inpatient and outpatient services.

Dr. Robert Channock has studied this agent, and I am sorry that he is not here to report on its characteristics. I am sure that the group at the National Institutes of Health know of the chimpanzee coryza virus, because it came from there.

Dr. Henry G. Cramblett, Washington, D. C.: Dr. Eichenwald, we can not estimate accurately the percentage of inapparent infections in the general orphanage population because the children were not under as close observation as the ones reported. However, by noting fever and clinical illness records during this period, we would estimate that 60% to 70% of the children from whom virus was recovered had clinical illness.

In the orphanage, only children 3 years of age or younger were under observation. Therefore, to date, we have no information on JV-1 virus infection in older children. Now, in regard to antibody titers in other age groups and in other children outside the orphanage, I might say this: Several sera from children of middle- or high-income family groups have been studied. Approximately 10% did have significant titers against JV-1 virus. The percentage of significant antibody titers in older children at the orphanage was somewhat higher.

We know nothing about the infection in adults.

Dr. Cooke, the viruses that you mentioned are not related to JV-1 virus.

**Relationships of Measles and Distemper: Pathological and Immunological Data.** JOHN M. ADAMS, M.D.; DAVID T. IMAGAWA, Ph.D.*; DAVID L. CHADWICK, M.D.*; EMILY H. GATES, M.D.,* and MIYE YOSHIMORI, M.S.,* Los Angeles.

Although measles and distemper, both virus diseases, have many epidemiological and clinical similarities, the pathological and immunological relationships will be emphasized in this report. A distinctive pathological picture is produced by the distemper virus in dogs and ferrets. Pulmonary lesions are characterized by proliferative changes in the lining epithelium, with giant-cell formation. The infiltrative reaction is largely mononuclear. Cytoplasmic and intranuclear inclusion bodies are most commonly found in bronchial and alveolar cells. They are often situated near the nucleus; they are usually round or oval but may be pleomorphic and vacuolated. This description may be applied to the pulmonary pathological findings in patients who have died of measles.

In tissue culture studies employing HeLa, KB, and Hep-2 cells the measles virus has been shown to cause characteristic cytopathology, with multinucleated giant cells and cytoplasmic and intranuclear inclusion bodies. These same changes have been produced experimentally in ferrets by distemper virus and the classical Warthin-Finkeldey cell has been found in the pharyngeal and tracheal tissues.

In HeLa cells cultures in which measles virus produces a distinct cytopathogenic effect, neutralization by specific canine distemper antiserum has been observed. Serums from ferrets immunized with avian or mouse-adapted strains of distemper virus inhibited growth of measles virus. Dilutions of serum up to 1:20 and rarely at 1:40 have caused this neutralization. Control serums from 20 normal preimmunization ferrets failed to exhibit the presence of any neutralizing antibody. Serums obtained from human beings during the acute phase of measles failed to neutralize measles virus in dilutions of less than 1:10, whereas convalescent serums contained antibodies in dilutions of 1:40 and 1:80. Complement-fixation studies with measles virus have shown significant titer rises up to 1:256. Significant rises by the CF test have been found in a few persons who have sustained a mild undifferentiated respiratory illness without a rash. Many of these persons have a history of measles.

Three different experiments with ferrets immunized with measles virus have been partially successful in confirming the neutralization studies in tissue culture. When these animals were challenged with virulent distemper virus, evidence of protection was revealed by prolonged incubation periods and survival of 8 of 20 animals. Sixteen control animals all died of typical distemper. One control animal survived the severe illness caused by the distemper challenge and subsequently was shown to have measles antibody. In a different experiment, distemper virus was successfully neutralized by specific measles antiserum. Employing the mouse-adapted strain of distemper virus, newborn mice were protected completely by the specific measles antiserum prepared in ferrets, whereas the preinoculation serum of the same animals failed to show any neutralization and all of the mice died of distemper. A similar experiment, employing human convalescent measles serum, has been equally effective in neutralizing the mouse-adapted distemper virus in newborn mice. A significant increase (more than fourfold) of antibody titer was found in the convalescent serums. These results suggest that common antigenic components are shared by the viruses of measles and distemper.

**Experimental Transmission and Trials of Passive-Active Immunity in Viral Hepatitis.** SAUL KRUGMAN, M.D.*; ROBERT WARD, M.D.; JOAN P. GILES, M.D.,* and A. MILTON JACOBS, M.D.,* New York.

Studies of endemic hepatitis at an institution for mental defectives were designed to answer these questions:

1. Would γ-globulin prevent its spread, and, if prevention occurred, would the effect be transitory or would it be prolonged in such a way as to suggest "passive-active" immunity (Stokes)?

2. Could "passive-active" immunity be induced experimentally in small isolated groups by injecting γ-globulin and then feeding hepatitis virus?

Results to date (June 14, 1957) have been as follows.

1. The first trial of γ-globulin (0.01 cc. per pound) seemed to have reduced the incidence of hepatitis: During the period of 31 weeks following its injection, the attack rate was 7.5 per 1000 in the γ-globulin group and 20 per 1000 in the control group. This difference appears to be significant.

A second trial of γ-globulin in a larger dose (0.06 cc. per pound) was followed by a more impressive reduction in the incidence of hepatitis. During the period of 20 weeks following its injection, the attack rate was 1.7 per 1000 in the γ-globulin group and 12.9 per 1000 in the control group.

The protective effect of γ-globulin, although not as complete as that reported by Stokes et al., was more long-lasting than would be expected from passive immunity alone.

2. The induction of experimental "passive-active" immunity was carried out as follows:

* By invitation.

(*a*) Preparation of virus. The virus was derived from stools collected from patients at the institution in the early stages of hepatitis with jaundice. A suspension was prepared and made bacteria-free by centrifugation, by addition of antimicrobials, and by heating at 56 C for one-half hour. Safety tests in tissue cultures, baby mice, and monkeys showed no harmful agents.

(*b*) Titration of virus. The stool suspension was titrated by mouth. Starting with the highest dilution, it was fed to groups of 5- to 10-year-old subjects newly admitted to an isolation unit. Mild hepatitis with jaundice resulted in 18 subjects receiving various amounts. The 50% infectivity end-point was about 1 gm. of stool. The incubation periods were unusually long for infective hepatitis, ranging between 39 and 67 days.

(*c*) Trial of "passive-active" immunity. Ten of fifteen subjects were given γ-globulin, 0.06 cc. per pound, followed within a half hour by ingestion of virus; five received virus alone. Of the 10 subjects receiving the combination of γ-globulin and virus, only one developed very mild hepatitis. Four of the five controls receiving virus alone developed mild hepatitis. Three months later the entire group was challenged with active virus. This study is still in progress.

3. In a recently completed experiment the following observation was made: Four of six subjects who were not fed virus (but who were intimately exposed to ten subjects who were fed active virus) developed hepatitis with jaundice after incubation periods of 60, 63, 67, and 71 days. Of the 10 who were fed virus, 5 developed the disease after 39, 41, 46, 60, and 71 days.

If the true incubation period is 40 days, then the occurrence of hepatitis in the control subjects after 60 to 71 days suggests that they acquired the virus about 20 days after the experimental group was fed. The implication of these observations is that there may be an "alimentary tract phase" with multiplication of virus at the half-way point in the incubation period—20 days after feeding and 20 days before onset of jaundice.

4. A titration of unheated virus was started. The results indicate that the incubation period after feeding of virus is not affected by heating at 56 C for one-half hour.

## Discussion

Dr. Paul Wehrle, Syracuse, N. Y.: Stimulated by these trials of Drs. Krugman and Ward and by some of Dr. Stokes' earlier observations, Dr. Hammon and I became curious as to whether there was something else in large pool γ-globulin preparations that might be responsible for the persistent type of immunity that has been described in these studies. The possibility of active immunization seemed reasonable, since statistically, with donor numbers of the size that went into the preparation of the large pool of plasma that was subsequently fractionated, at least SH virus might be present, and possibly the other agent as well. It also seemed possible, from data provided by fractionation of plasma containing other viral agents, that perhaps not all of this material might be removed. Traces of clinically inactive material may remain. Consequently, we reviewed data from the original field trials of γ-globulin against poliomyelitis in Utah and in the Iowa-Nebraska areas, where approximately 10,000 children had received doses of γ-globulin, from 4 to 11 cc., during 1951 and 1952. In these areas there were approximately 10,000 recipients of gelatin who were innoculated at the same time, and a roughly equivalent number of observed controls. The cases considered were hepatitis patients reported to the local health departments in these areas. It was interesting that no hepatitis was reported for approximately a year and a half following the field trials in either of the areas. However, after this lapse of time, cases of hepatitis began to occur with approximately equal frequency in the γ-globulin recipients as well as in the gelatin recipients and in the control groups. Thus, it seems unlikely that the large-pool γ-globulin conferred any long-lasting or permanent active immunity.

I wonder if Drs. Krugman and Ward and other members of the group contemplated challenging the are to be congratulated on this most interesting γ-globulin recipients in this particular study with their virus in order to further indicate the absence of any active principle in the γ-globulin itself.

Dr. Joseph Stokes Jr., Philadelphia: I think that Dr. Krugman, Dr. Ward, and their associates work.

One bit of evidence in favor of the intestinal infection was obtained by studies of Dr. Tracy Mallory and others in the Mediterranean area, where it was shown during large epidemics, in persons who were in the incubation period and who died by homicide, by suicide, or by accident, that the duodenum was often filled with mucus.

The length of the incubation period is of particular interest here. Hundreds of epidemics have occurred in which the incubation period has been carefully noted, and in most epidemics it has ranged from 18 to 35 or 40 days. In the present studies there was an incubation period of over 39 days even with the unheated material, suggesting that this may be a somewhat different virus from the usual epidemic hepatitis virus. I was wondering, therefore, if the present authors have taken blood from any of their patients and given this by mouth or given it parenterally to see whether the incubation period might be different under these conditions.

Also, it would be of interest to know whether the patients that had the γ-globulin all had jaundice or whether several of them had hepatitis without jaundice. One point suggesting that this may be a slightly different strain of virus is the fact that the γ-globulin required to give complete protection was as great as 0.06 ml. per pound, and even that amount did not seem to give complete protection. Although these cases may have been hepatitis without jaundice, I think that often persons can get mild hepatitis without jaundice with large doses, after which, as a rule, the persons in question have been immune.

The question may well be raised as to whether this is a really adequate method of immunization. We have also felt that this might be a worth-while method. I think it is well to remember that most of the drinking water of the country, after all, is stool filtrate, which is really highly diluted but at the same time is one method by which many persons probably become immunized. Water is somewhat difficult to free of hepatitis virus by the ordinary methods. The same is probably true of another intestinal virus, namely, poliomyelitis virus. In other words, there may well be an occasional "break through" with infection from water.

Dr. Heinz F. Eichenwald, New York: I think the studies are very beautiful and may provide answers to many of the problems presented by this disease. With the Communicable Disease Center of the Public Health Service, and leaning heavily on Dr. Stokes' advice, we studied a number of naturally occurring outbreaks and tried to use these to answer some of the questions which have been approached so much more elegantly by Dr. Ward and Dr. Krugman.

I think one experience might be worth mentioning. An epidemic occurred which was centered entirely around a single school. The children acquired their infection in the school by "person to person contact" and then went home and gave it to their parents. We were fortunate in arriving at a sufficiently early time to be able to give half the children in the school γ-globulin. Because there was not enough γ-globulin to give to all of them, the other half did not receive any. Then we followed households of the treated and untreated groups, and to our surprise the secondary attack rates among the adults in these families were almost identical, whether the children had received γ-globulin or not, while the rate of hepatitis among the γ-globulin recipients had been reduced more than twentyfold. A dose of 0.01 cc. per pound was used. I should like to ask Dr. Krugman if in his experience he has been able to get evidence that a γ-globulin recipient subsequently exposed to hepatitis is still capable of excreting the virus in an infectious form and whether a child who has received γ-globulin and then the virus does develop transient liver abnormalities on the basis of chemical tests.

Dr. Saul Krugman, New York: There are at least three possible explanations for the prolonged protective effect following the inoculation of γ-globulin: (1) passive-active immunity, as postulated by Dr. Stokes; (2) persistence of passive antibody for a prolonged period, and (3) the possibility that small amounts of virus may have been present in the γ-globulin. I am indebted to Dr. Wehrle who, in his discussion, provided us with data which suggest that γ-globulin is free of active hepatitis virus. The persistence of passively administered antibody beyond four weeks would be very unlikely. The most attractive hypothesis thus far is that of passive-active immunity, advanced by Stokes. Our future studies may shed more light on this question.

In answer to Dr. Wehrle's question pertaining to the challenge of the recipients of γ-globulin in the institution at large—this has not been done.

Dr. Stokes has suggested that this agent may be a different virus. The disease, however, is clinically identical to the cases of infectious hepatitis one sees in hospital practice. The only difference appears to be in the prolonged incubation period. Our studies with potentially active serum, Dr. Stokes, are planned for the future.

Dr. Eichenwald has asked whether the γ-globulin recipients are capable of excreting the virus and whether we have performed follow-up liver chemistry studies on the institutional cases of hepatitis. Thus far, we have done neither of these studies.

Our limited isolation facilities and the long incubation period of the Willowbrook strain of hepatitis virus have restricted the number of studies which we can carry out in a period of time.

**Congenital Toxoplasmosis: A Study of One Hundred Fifty Cases.** Heinz F. Eichenwald, M.D.,* New York. Introduced by S. Z. Levine.

With increasing application of serologic diagnostic methods, it has become apparent that congenital toxoplasmosis is a disease of variable symptomatology and severity, often difficult to recognize on clinical grounds alone.

Of 150 infants with proven congenital toxoplasmosis studied in the past 10 years, approximately one-third showed signs and symptoms of an acute infectious process, with splenomegaly, jaundice, hepatomegaly, anemia, chorioretinitis, and abnormal spinal fluid as the commonest findings. The so-called "classical triad" of toxoplasmosis, consisting of choroiditis, intracranial calcifications, and hydrocephalus, was demonstrated in only a small proportion of the patients.

These data suggest that toxoplasmosis must be considered in the differential diagnosis of almost every obscure illness during the neonatal period.

* By invitation.

Most of the patients were followed closely from birth to 5 or more years of age. The over-all mortality rate was 12%. However, 90% of survivors showed mental retardation; almost 75% developed convulsions, spasticity, and palsies, and about one-half had severely impaired sight.

A group of 14 infants with the acute disease were treated with a combination of sulfadiazine and pyrimethamine. Although this method of therapy appeared to have some beneficial effect in shortening the course of the acute illness, its efficiency in the prevention of neurologic defects appears slight. A similar study using a therapeutic regimen of sulfadiazine and anti-Toxoplasma sera similarly failed to reveal striking beneficial results.

### Discussion

DR. JOSEPH STOKES JR., Philadelphia: I should like to ask Dr. Eichenwald whether he has any knowledge concerning the age range of those affected in the United States. I was much interested in discussions by Dr. Siim and others last summer in Copenhagen. Apparently they have detected much more toxoplasmosis in that area, transmitted from animals directly to man, and have found it over a wide age range. I should also like to hear something about the variety of symptoms at different ages, particularly as to how the question of lymphadenitis may give some clue to the early symptoms, and therefore toward treatment of the disease. This is one of the early signs which in Scandinavia they believe may cause some suspicion of such infection.

DR. C. HENRY KEMPE, Denver: I should like to know your clinical observations on the mothers of these children: predominant age range, occupation, racial background, previous clinical illness, and any other clue as to pinning down the likely mother.

DR. HEINZ F. EICHENWALD, New York: Dr. Stokes brings up a very interesting point which has bothered us also. Being a pediatrician, I have had very few adults suspected of having toxoplasmosis referred to me. However, we have carefully examined the mothers of the congenitally infected children, and this, then, brings us also to Dr. Kempe's question. These mothers not infrequently give us a history which suggests that they might have had toxoplasmosis in the clinical form which the Scandinavian investigators have described. These women will apparently occasionally go through a phase where they show lymphadenopathy, occasionally limited to only one or two nodes, plus a minor illness of some sort. Just before I came here I saw a slide from a woman who had had a biopsy performed during her pregnancy because of a large tender node. She delivered a child with acute toxoplasmosis two months thereafter. In this node there were Toxoplasma organisms. Unfortunately, we have the disadvantage of not being able to see these mothers when they have the acute disease; we only see them after they have given birth to an infected baby, and we are therefore frequently months too late.

As to the epidemiology of the disease, this has interested us greatly. We have found this disease in offspring from all social groups, ranging from the child of a Dean of a medical school to the migrant Puerto Rican population in New York. We have attempted to correlate social factors, age, the presence of dogs, cats, birds, mice, vermin, dirt—anything we could get—to the incidence of toxoplasmosis and have been unable to do so. There is not a single factor known to us which would indicate that one mother is more likely to develop toxoplasmosis than another.

**Rumination—A Psychosomatic Disorder of Infancy.** JULIUS B. RICHMOND, M.D., and EVELYN J. EDDY, M.D.,* Syracuse, N. Y.

The pediatric literature in recent years has been almost devoid of any discussion of the syndrome of rumination. Because of the confusion in the literature concerning the nature of this disorder, a study of four patients and their families was undertaken. Some of the diagnoses considered prior to admission were adrenal insufficiency, pyloric stenosis, food allergy, and severe feeding problem. In each patient abnormal behavior was observed in addition to the symptom of rumination. Such behavior will be briefly illustrated by a motion picture film.

The study of these patients indicated considerable disturbance in the relationship between mother and infant. In each instance it would appear that the baby received insufficient maternal care in the form of comfortable physical contact and gratification. It is postulated that the symptom is an attempt by the infant to substitute gratification from within when such gratification is not forthcoming from without the organism in the form of comfortable and stimulating experiences with a mother figure. The response of these infants to such care will be described.

The study of the mothers of these infants has thus far revealed the following: (1) striking immaturity, reflecting itself as an incapacity to accept and to provide care for the baby—this immaturity was sufficiently severe to suggest prepsychotic behavior or the diagnosis of psychopathic personality; (2) a fear that the baby will die, and (3) marital difficulties. The specific relationship of these findings to the development of rumination in these infants is not as yet clearly understood. The possibility of constitutional differences in autonomic

* By invitation.

function as a predisposing factor has been considered.

The reversal of symptoms during treatment has been striking. With the interruption of the mother-infant relationship by hospitalization of the baby and the provision of stimulating care by a substitute mother figure, these infants have gradually ceased to ruminate. During hospitalization the mother experiences some relief from her anxiety concerning the physical care of the baby, and through her relationship with the staff she develops a feeling of confidence concerning her ability to care for the infant. On discharge from the hospital these babies have not resumed ruminating. Extensive psychiatric therapy for mothers has not been undertaken thus far. Supportive therapy in the pediatric setting however, has seemed to provide enough ego support for these mothers to carry on with some degree of adequacy.

## Discussion

Dr. Milton J. E. Senn, New Haven, Conn.: I should like to congratulate Dr. Richmond on presenting this interesting discussion of human behavior before the pediatric audience. It seems to me that the problem of rumination which confronted us 20 and 25 years ago was of a different nature, however. In those days we were concerned with rumination that we saw frequently, but the patients were not children of the age that Dr. Richmond presented today. Then we commonly saw young babies who ruminated and lost weight, and one of our great problems was attempting to get food into them and helping them retain the food long enough so that they could metabolize it. I believe that Dr. Richmond's patients were psychotic or prepsychotic. I share with him his pessimism for the future of these babies unless the parents get psychiatric treatment. Unless efforts are made to really help them beyond control of rumination their psychotic behavior will return, with symptoms more appropriate to an older age period.

Dr. Arthur H. Parmelee, Pacific Palisades, Calif.: I should like to voice the sentiment that Dr. Senn has just expressed. These cases presented today as ruminators are not the type that we used to call ruminators. It seemed to me that in the cases reported rumination was simply one part of a general picture of lack of adequate care or even of mental deficiency. Children who would develop rumination were almost invariably happy babies in the beginning. They were habitual vomiters first, but it was not true vomiting—I prefer to call it chronic spitting. This would start in the first month of life; then, after a few weeks or maybe a few months, you would see signs of rumination, but not all babies who were chronic spitters were ruminators.

Dr. Grulee in 1925 tried some experiments in which special nurses acted as substitute mothers, so to speak, and spent their whole time with three ruminators, keeping them happy, over a period of several weeks, and he gave it up after a while because it was an endless process. After that care was stopped, they began to ruminate again.

I think that we are dealing with quite a different thing here from rumination as we thought of it in the past.

Dr. Robert Kugel, Iowa City: I should like to ask Dr. Richmond whether he has seen this syndrome in children who are nonpsychotic and truly mentally retarded infants.

Dr. Giulio J. Barbero, Philadelphia: Dr. Richmond's paper on rumination as a severe psychosomatic disorder certainly summarizes our experience with this entity. It would appear that the pediatric literature has described the picture as episodic rather than as a progressive continuum with multiple physiological and psychological changes. In our patients with rumination there was a history of intense irritability, regurgitation, colic, sleep disturbance, and feeding difficulty in the first two to three months. Subsequently, there was a shift to progressive passivity and withdrawal within themselves. In early cases such gastrointestinal symptoms may be of transitory importance; however, in older cases the gastrointestinal symptoms are a physiological manifestation of a generalized underlying personality disturbance of severe nature. When symptoms do not subside in the first few months, either spontaneously or with help, then persistence and chronicity become our first clue that major damage to the child's development has taken place.

We have been interested in the early period, since our observations on infants in the first few months suggest that they react to stress with gastrointestinal symptoms and marked irritability at this period. Later, such infants go on to show more specific or psychic derangements, such as rumination, chronic bowel frequency, anorexia, and atypical development. Very little study and observation of such infants in both their early course and their later deviant development is available, and so much of our concepts of psychic and physiological disturbance comes from retrospective material. Dr. Richmond's paper can serve as notice for the increasing need for organized observation of the patterns manifested by these infants and the interaction with their parents.

Another problem of interest in rumination involves the lack of understanding of the physiological process of rumination itself. Movies of ruminating infants show little of the usual abdominal contractions which accompany the vomiting process. I believe that the fluoroscopic image in-

tensifier and cinefluorography might be helpful in further study of the physiological disturbance. Whenever we tried some x-ray or fluoroscopic examination of a ruminating infant, the rumination subsided at the time when the infant's attention was focused on the outside world. Thus, the status of the infant's capacity to show object relationships has to be taken into account during the performance of such studies.

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: I should like to comment on remarks that Dr. Senn and Dr. Parmelee made, since they tend to group themselves together.

I should not like to leave the impression that we have formulated a specific psychodynamic constellation in the mother—or in the mother-infant interaction—which is responsible for the syndrome. Rather, I feel that this, as well as some of the other neurotic behavior of infants and young children which I mentioned and illustrated, is responsive to the mother's emotional "distance" from the infant, particularly when the "distance" becomes more manifest after the time of visual maturation to the point at which the parents can be identified visually as the central figures in the life of the baby. Whether in years gone by this was because of poor social circumstances, poor education in infant care, or whatever, I think the same kind of lack of sensory stimulation for the infant may have prevailed in family circumstances in which the mothers were not so disturbed. This is why, in my introductory remarks, I suggested that perhaps the decline in the incidence of this disorder has been associated with improved social and economic standards, which in turn has reflected itself in better infant care generally. Therefore, I do not think that this condition is specifically due to severe psychiatric disturbances in the mother, but at the present time the mothers in well-situated social and economic groups tend to be remote from their infants only when their psychopathology is sufficiently extreme so that they can not engage in close mothering relationships with the infant.

I think Dr. Parmelee's comment that in years gone by many of these were happy babies is not incompatible with what I have suggested; nor is it incompatible with one of the points that Dr. Barbero brought up about the irritability of these infants. I think the important point is that these infants have had some of their most gratifying experiences early in the feeding relationship, and it is when they need more than this relationship, when they need much more stimulation and are not getting it, that they develop irritability and seek to re-create gratification by this process. This is obviously interpretative; we do not know what infants really think, but this is the best suggestion that I can make at this point.

Dr. Parmelee mentioned Dr. Grulee's study. In going back to that study not long ago I found it rather interesting that he, perhaps more clearly than anyone else, pointed to the neurotic nature of the disturbance. He did not seem to follow through on this, however. I would agree with Dr. Parmelee that these babies require a large amount of intensive nursing care. I perhaps did not emphasize this sufficiently, but stimulation in the environment will tend to minimize the act of rumination.

Dr. Kugel raised the question as to whether this syndrome does occur in nonpsychotic and retarded infants. At first, because of the kind of observation Dr. Parmelee made, that these were happy and often very alert babies, we were inclined to believe that maybe it was the brightness of the infant that caused him to select rumination as a symptom. However, this is not an adequate explanation, because in the institutions for mentally retarded, it is observed that retarded infants do ruminate.

Dr. Barbero raised some important issues. Physiologically what this process is, as I indicated, is rather difficult to determine. If one undertakes any manipulation of these infants one generally interrupts the process—the observation that Cameron made back in 1925. However, some of the newer techniques, as he has indicated, should make it possible to study the problem more effectively. I think that under all these circumstances we have to be extremely cautious about radiation hazards.

**Studies on Glycogen-Storage Disease: II. Column Chromatography.** RICHARD WAGNER, M.D., Boston.

In a previous study (reported at the meeting of the American Pediatric Society in Quebec, 1955) the presence in the peripheral blood of phosphorylated intermediates of the glycolytic cycle in glycogen-storage disease was demonstrated. The chromatographic studies carried out on deproteinized serum filtrates did not allow a quantitative evaluation, which appears to be essential in questionable cases of this enzymatic defect. In the present study the sugar phosphates were separated from whole blood or serum by ion exchange with the use of the borate complexes. Each borate fraction was studied by filter-paper chromatography, according to Hanes and Isherwood, and compared with the analogous fractions recovered from normal blood. Glucose-1- and glucose-6-phosphate and hexose-1,6-diphosphate were identified in both normal and the patients' material; fructose-6-phosphate, only in the patients' serum, and $\alpha$-glycerophosphate, only in the patients' whole blood. The Seliwanoff reaction in deproteinized serum filtrates of patients with glycogen-storage disease is frequently positive.

Organic phosphorus determinations in the individual borate fractions revealed a considerable preponderance in glycogen-storage disease, particularly for the glucose-6- and fructose-6-phosphate fractions. This was demonstrable even in a relatively mild case of the disease, where it had diagnostic value. Sugar was determined in the borate fractions by the anthrone method. However, the determination of the organic phosphorus is more adequate for the study of phosphorylated intermediates in the blood. An attempt at calculating the sugar phosphates from the organic phosphorus obtained did not agree with the observed anthrone values, since the method is not specific enough.

The presence of reducing phosphorylated intermediates in the blood of patients with glycogen-storage disease explains some of the peculiarities of the ailment. The low, in some cases even missing, reducing value of the blood is the result not only of the absence of glucose but also of the presence of sugar phosphates of lower reducing power than that of glucose.

### Discussion

DR. ALEXIS F. HARTMANN, St. Louis: I should like to ask Dr. Wagner whether I am correct in assuming that the data obtained were obtained from a child with the liver-kidney variety of glycogen storage disease where the enzyme defect was the specific glucose-6-phosphate, and whether he has had a chance to make similar observations in the generalized type where cardiac and skeletal muscle are also involved.

DR. RICHARD WAGNER, Boston: All cases were of the hepatonephromegalic type (von Gierke). I had no opportunity to study cases representative of the other three types. Two of them show abnormal glycogen structure, demonstrated by Cori cycles with stepwise enzymatic degradation. Type 2 is a generalized glycogenosis erroneously named the cardiac type of the disease. The enzymatic defect is unknown. It is fatal within the first two years of life, in contrast to the hepatonephromegalic cases, in which the patient may survive. Our first patient, reported in 1921, developed diabetes mellitus later in life. In Type 3 an abnormal structure of liver and muscle glycogen was detected. It is considered a defect of the enzyme amylo-1,6-glucosidase (debrancher). Only one case has been studied so far. In Type 4 the glycogen is likewise abnormal. The enzymatic defect is one of amylo-(1, 4→1,6)-transglucosidase (brancher). A case of D. H. Andersen with accumulation of glycogen in the liver and in the reticuloendothelial cells and with familial cirrhosis of the liver belongs into this group (Cori, G.: Harvey Lect. 48:145, 1952-1953).

**Insulin-Producing Capacity of the Pancreas in Children with Diabetes Mellitus.** R. KLEIN, M.D.; J. MARKS, M.D.,* and I. A. MIRSKY, M.D.,* Pittsburgh.

The relatively small amounts of exogenous insulin required early in the course of diabetes mellitus in the child and the marked decrease in such insulin requirements which may follow the initial period of treatment suggest that the pancreas is still capable of producing insulin at the onset of the clinical disorder. Subsequently, however, pancreatic exhaustion and irreversible insulin insufficiency ensue.

The length of the interval between the onset of the metabolic derangement and the exhaustion of the islet tissue was determined by utilizing hypoglycemic agents which are insulin-dependent. Tolbutamide and indole-3-acetic acid are such agents, since they produce hypoglycemic responses only in the presence of active beta cells. Whereas tolbutamide appears to act primarily via stimulation of the islet tissue and secondarily by inhibiting the action of insulinase and other enzyme systems, indoleacetic acid appears to act only through its insulinase inhibitory activity. The response to the oral administration of standard doses of these agents was determined at intervals after the diagnosis of diabetes mellitus had been made. Five-hourly samples of capillary blood were taken after the administration of each agent.

The magnitude of the blood sugar depression in response to these agents correlated inversely with duration of disease. The patients were divided into four groups by duration of disease: less than 6 months, 6 to 23 months, 24 to 47 months, and more than 48 months. The mean responses for these groups fell progressively. Although response correlated with duration even after two years, only one child with diabetes of more than two years' duration responded to these agents with a depression of blood sugar significantly greater than that of diabetic children who were given placebos only. A fall in blood sugar of 20% in a fasting diabetic at four or five hours is not evidence of a response to any drug, as it occurs spontaneously.

These studies indicate that at the onset of the diabetic syndrome the pancreas of the child is still capable of producing insulin (relative insulin insufficiency) but that subsequently this capacity is lost.

Three of four patients with early diabetes requiring 10 to 30 units of insulin have been successfully maintained on indoleacetic acid alone. However, since they remained glycosuric (approximately 20 gm. per day), this has been discontinued, although it should be tried again with the addition of exogenous insulin.

* By invitation.

An attempt to avert pancreatic exhaustion by the administration of indoleacetic acid to diabetic children in the period when they require no or very little insulin is being tried. Since these children can spontaneously go a year or more without needing insulin, it is too early to comment on this possibility.

### Discussion

DR. A. L. CHUTE, Toronto: I think that this is a field which certainly is one of great interest to all those who have had anything to do with juvenile diabetes. I think it was well shown in very early days of the discovery of insulin that there were two methods by which the islets could be protected. Best and his group showed that giving partially depancreatized animals a high-carbohydrate diet led to pancreatic exhaustion. Such animals put on a high-carbohydrate diet, however, could be protected by insulin, and I think that this is something we should not forget—that both diet and insulin are capable of protecting islet-cell function. I think that, because the juvenile diabetic loses his islet-cell function so rapidly, there has been a great tendency, particularly because of the psychological factors involved, to ignore these rather important features. However, it seems to me that if we are ever to do anything fundamental for the juvenile diabetic, it is in this field that we must concentrate, and I would suggest that these two factors of diet and insulin should be used to supplement any other treatment, such as indoleacetic acid or other substances which may tend to prolong the action of insulin and therefore still further improve the resting of the islet cells.

DR. ROBERT L. JACKSON, Columbia, Mo.: It is gratifying that we are beginning to understand better the reasons for the relatively low exogenous insulin requirement for the short period after metabolic restoration. As Dr. Klein briefly mentioned, another factor which is very important needs to be stressed. During this period of lower insulin requirement, there is little or no growth in height, after which there is a period of increasing insulin requirement and an acceleration of linear growth. Recently it also has been found that antibodies to insulin develop after insulin therapy. I should like to ask the authors if they have any data to evaluate this factor. Also, I should like to know how they controlled physical activity during the period that the blood determinations were being made. Lastly, I should like to know if they have any data about the new nonsulfonylurea hypoglycemic agent known as DBI.

DR. FRANCIS SCOTT SMYTH, San Francisco: I should like to know whether there is enough information by which a contrast can be made with regard to the child with long-standing diabetes who has been under strict glycemic control and a child who has not.

Would a patient with a relative hypoglycemia show less pancreatic exhaustion and respond to these agents better than the patient who maintained high blood sugar levels? Secondly, does Dr. Klein know of any experiments on the subtotally pancreatectomized dog which might suggest a diabetogenic effect of these agents?

DR. MARVIN CORNBLATH, Baltimore: I should like to ask Dr. Klein whether he investigated any quantitative aspects, using different doses of tolbutamide, and whether he could get any estimation of circulating insulin in this way. Since all the insulin assay methods available are so notoriously bad, perhaps he could use this tool, which he has described so beautifully to us today, either by coupling it with carbohydrate feeding or by using various doses, to estimate circulating insulin.

DR. VINCENT C. KELLEY, Salt Lake City: I should like to ask Dr. Klein whether he has had any experience with the stabilization of the very labile diabetic with tolbutamide. This may be an important aspect of tolbutamide supplementation of insulin therapy. I think that all of us hoped at one time that we would be able to replace insulin with some oral medication. At the present time most of us are pessimistic about this possibility. However, in our clinic we have had one very dramatic experience with alleviating symptomatology in a child who was repeatedly in insulin shock. When tolbutamide was added to her therapy the insulin requirement was not reduced very much, but the child now has gone for about eight months without one episode of shock, whereas previously she had been in shock repeatedly.

DR. ALEXIS F. HARTMANN, St. Louis: I should like to ask Dr. Klein whether, when apparently there was partial or a beginning recovery of tolerance, he saw by other means, such as the metabolic glucose-insulin ratio, improvement of tolerance, and, if so, how much was such a ratio affected?

DR. ROBERT KLEIN, Pittsburgh: Dr. Chute, I think that the protection of the islets with a low-carbohydrate diet or, more appropriately, I think, with insulin sounds very reasonable. The difficulty is that we have never been able to really do this. I think Dr. Jackson comes closest with his particular group that he can indoctrinate in the special regimen. However, over the long term, as far as I can tell from the literature, nobody has effectively done this. In the 20-year follow-up strictly controlled groups have as much trouble as those which are treated more tolerantly.

Dr. Jackson, if I may, I should like to put Dr. Kelley's question in there too. This question of development of insulin resistance I think is very

pertinent. I have a hunch that this is the result of developing antibodies to the insulin. I think that this occurs probably frequently, but I have not enough evidence. We have demonstrated for the first time precipitating antibodies in a patient with resistant diabetes requiring over 200 units of insulin.

Dr. Kelley's question. We gave that patient tolbutamide, and I can not speak definitively, but I did not notice that it helped at all. This boy would have marked hyperglycemia, even with the tremendous dose of insulin we gave him, and then periodically he would go into shock. I think this must have something to do with the inactivation of the insulin by the antibodies, and later release. We are now testing all our diabetics to see if we can demonstrate antibodies. I can not answer the problem. He was certainly not helped, but, as in all the adults reported in the literature, his resistance spontaneously disappeared. We did change types of insulin, but I am not convinced that this made any difference, though it might have.

I have no information, Dr. Jackson, on the new hypoglycemic agent. As I understand, this is supposed to rid the liver of glycogen, and I would be afraid to use it in children.

You put your finger on one of the "hookers" in our tests. Activity was not very well controlled. We tried to minimize it. These were all ambulatory patients, and I think they are probably more active when you sit on them than when you let them have free activity, but we tried and it was not very successful.

Dr. Smyth, the initial level of blood sugar showed some tentative correlation with the result, but it is in the opposite direction; that is, the lower the blood sugar initially the better the response. I would assume that this meant that this was perhaps a milder diabetic or earlier, and certainly it had no statistical significance. I don't know that subtotally pancreatectomized dogs have been tested with any of these agents. However, other animals partially pancreatectomized have shown responses more nearly akin to the normal than to the diabetic. Incidentally, we have seen one or two patients who have very mild diabetes. The patient would come into the hospital for tonsillectomy and adnoidectomy, or something of that sort, and would be found to be "spilling" a small amount of glucose. These patients I have in mind went for over a year following that without requiring any insulin. Though they were growing and doing well, they had abnormal glucose tolerances. These two patients had perfectly normal responses to tolbutamide in that they had very rapid fall in blood sugar in the first half hour.

Dr. Cornblath, we have tried different doses. The dose of tolbutamide that we finally used was the standard 50 mg. per kilogram. Increasing it made no difference in the initial blood sugar fall. It does make some difference in the four- and five-hour level. The indoleacetic acid we gave in doses of 140 mg. per 100 Cal., which is roughly the same in the large children but is twice as much in the small children. We are totally unable to use this as a method of insulin assay with our modest information.

Dr. Hartmann, the only information that we have in the period of partial recovery is merely that the patients' insulin requirement had dropped, they were growing well, and they were healthy. We did not at this time do an insulin-tolerance test. We have, however, done bank tolerances at this time, and they have a very nice response to fasting.

**Needle Biopsy of the Liver and Cholangiography as Aids in the Diagnosis of Prolonged Jaundice in Infancy.** ROBERT KAVE, M.D.*; BERNARD M. WAGNER, M.D.*; C. EVERETT KOOP, M.D., SCD.,* and JOHN W. HOPE, M.D.,* Philadelphia. Introduced by JOSEPH STOKES JR.

The observation of a 3-month-old infant who had already developed ascites, esophageal varices, and biliary cirrhosis secondary to atresia of the bile ducts has persuaded us of the need for early accurate diagnosis and definitive treatment in this syndrome. Of similar import is the experience in this clinic that the only entirely curative results in this condition were achieved in infants upon whom operation was carried out prior to the age of 2 months.

On the other hand, there are factors leading to delay in diagnosis. There is a justifiable reluctance to subject the infant who may be suffering from hepatitis to the risks entailed in exploratory laparotomy, particularly in view of the fact that approximately 80% of them may be expected to recover spontaneously, whereas only 10% of patients with biliary atresia prove to have operable lesions. A greater deterrent to prompt diagnosis of biliary atresia is the disturbing frequency with which findings in the histories and laboratory examinations of these patients suggest hepatitis as the correct diagnosis and lead to delay in or failure to recognize the correct situation prior to the development of irreversible biliary cirrhosis. Such misleading data as a history of the passage of yellow stools for weeks or months after birth, of onset of jaundice at 2 to 3 months of age, and of complete clearing of jaundice after its establishment are unfortunately too common. Laboratory findings erroneously suggesting hepatitis are not infrequently encountered, such as high initial serum bilirubin values which fluctuate or fall with or without cortisone administration, positive tests for urobilinogen in urine or stool, and positive tests indicative of hepatocellular damage.

* By invitation.

For these reasons, a study of needle biopsy as an adjunct to diagnosis in infants with prolonged jaundice has been carried out. In those patients in whom biopsy and other findings are suggestive of extrahepatic obstruction, limited surgical exploration combined with cholangiography is superior from the standpoint of accuracy of diagnosis and is better tolerated than extensive anatomical delineation of the biliary tract.

The findings in six patients in whom needle biopsy correctly clarified the clinical picture in the face of contrary evidence are presented. It appears that needle biopsy offers a safe means of establishing an early diagnosis of biliary atresia, thus obviating prolonged periods of observation, which are likely to result in the development of irreversible biliary cirrhosis. In some instances of hepatitis the procedure will yield material permitting avoidance of unnecessary surgery.

The limitations of needle biopsy, as well as its complications and contraindications, will be discussed. In addition, a plan for the management of infants with prolonged jaundice will be outlined.

## Discussion

DR. DAVID YI-YUNG HSIA, Chicago: I should like to ask Dr. Kaye the relative role of cortisone therapy in comparison with needle biopsy of the liver in the diagnosis of neonatal hepatitis versus biliary atresia. I am wondering whether these patients should be subjected first to a short period of cortisone therapy before needle biopsy is resorted to, since the former procedure is much less hazardous than the latter.

DR. ANDREW SASS-KORTSAK, Toronto: I should like to congratulate the speaker for taking such a bold step in dealing with this very difficult problem. I think many of you in this audience have had the experience of worrying over babies like the ones reported here. What I would like to emphasize is that, in spite of the excellent results the authors obviously are having with liver biopsies in the differential diagnosis, one should not rely on one single method but use an approach of many angles in dealing with these patients. For example, in spite of the general belief that liver-function studies are of no use in differentiation between the hepatitis type of lesion and atresia of the bile ducts in the young infant, we found that a distinct group of the cases with hepatitis type of lesion will have positive tests of parenchymal liver function. We think, therefore, that detailed liver-function studies should still be carried out on these infants.

I should like to mention also that we have never encountered such a severe type of cirrhosis at the early age of 2 months as that presented by the authors. These cases must obviously be very rare.

Finally, I should like to ask the authors for a more detailed outline of the method used in operative cholangiography. We had some difficulty in obtaining filling of the hepatic ducts.

DR. ROBERT BRENT, Philadelphia: At Walter Reed Hospital we have had extensive experience with needle liver biopsy, and in many cases of jaundice in the first six months found it to be disappointing for the differentiation of biliary atresia from hepatitis. Because of this, we have used the new radioactive dye, rose bengal, to establish patency of the bile ducts. Because of the concentrating action of the liver, as little as 1μc to 4μc can be used. The dye is excreted in the feces, and the feces are examined for radioactivity. We then hydrolyze the feces with sodium hydroxide and count an aliquot in a scintillation counter to determine the percentage of administered radioactivity which comes out in the feces. In several cases in which the liver biopsy has resulted in a diagnosis of biliary atresia, the fecal excretion of radioactive rose bengal had been very high, even though these particular infants had the classical white or clay-like stools of biliary atresia. Both infants cleared, which confirmed the tests of biliary patency. Furthermore, there is a direct correlation of urine excretion of $I^{131}$ and the length of time the intact dye remains in the liver. Thus, in cases of "biliary atresia" we have shown that eventually all the $I^{131}$ is separated from the dye molecule and excreted in the urine. Further work may demonstrate that a high level of radioactivity in the urine will indicate complete obstruction. At the present time we have no cases of complete atresia in which more than 2% of the administered radioactivity was excreted in the feces. As a corollary, the urine plus thyroid radioactivity in the first 24 hours will be more than 10% of the administered radioactivity in complete obstruction. If we are able to demonstrate that some of these cases of "biliary atresia" are necrotizing hepatitis with complete destruction of the biliary tree we may be able to add a great deal to our knowledge of jaundice in the first six months. The way that this may come about is by finding cases of jaundice in the first few weeks of life in which the dye is excreted; then, as time goes on and the hepatitis progresses, these children no longer excrete the dye and have complete obstruction and so-called "biliary atresia." The test easily demonstrates biliary patency in cases which appear to be complete obstruction, and for that alone it is of value.

DR. W. A. NEWTON JR., Columbus, Ohio: I should simply like to tell about our experience in Columbus, where our surgeons have taken a further bolder step in this important problem. They have emphasized to us the need for determining the presence of biliary atresia early, since we have seen several children in the past few years who

have had a repairable lesion of the extrahepatic biliary tree who have developed irreversible cirrhosis and died; these could have been cured if treated early. Stimulated by this experience, we reviewed the liver sections of 29 children with obstructive jaundice in the neonatal period, and we were able to distinguish by biopsy alone whether or not a patient had hepatitis or extrahepatic biliary atresia. Since this time, some 10 patients with obstructive jaundice in the early period of infancy, usually before 2 months of age, have been subjected to an operative procedure in which a wedge liver biopsy specimen has been taken instead of a needle biopsy specimen, as Dr. Kaye has reported. Thus far, in each case we have obtained an adequate tissue sample and have been able to diagnose each patient's problem accurately. This was done as a very brief operative procedure, requiring at the most 45 minutes of local or very light general anesthesia. At the same time, a cholangiogram was done. If the child's problem was shown to be biliary atresia, then a second operative procedure was planned; if it was hepatitis the child was treated medically and showed no adverse effects from this procedure.

We feel that cholangiogram and biopsy are both needed to establish correct diagnosis in every case and should be done by 4 to 6 weeks of age in any patient with complete obstruction to flow of bile into the gastrointestinal tract.

DR. BYLE, New York: I should like to find out whether Dr. Kaye used a subcostal or an intracostal approach for the biopsy and what precautions if any he took so the baby would not fret or squirm during the actual biopsy.

DR. DANIEL STOWENS, Washington, D. C.: We have had approximately 220 cases of biliary atresia to study at the Armed Forces Institute, and there are certain points that I think need clarification. First, let me say that I am in complete agreement with the author that needle biopsy is far preferable to any other form of diagnostic tool, as long as one realizes its limitations. As an aside, we have done well over 800 biopsies, with luck on our side or something, with no trouble whatsoever. Now, the author has pointed out fibrosis in all of his cases; that is somewhat at variance with our findings. Fibrosis is a late finding in congenital biliary atresia, usually not occurring until after 4 months of age. Early in the course of the disease our diagnostic criteria include the architecture of the liver as a whole, which we find to be disrupted; the general lack of bile stasis, which is a peculiar thing in these children; the abnormality of the ducts themselves, and the vascular abnormality involving the hepatic artery, which always appears to be somewhat hypertrophied. As far as differentiating this from hepatitis is concerned, or the giant-cell transformation of the liver, as we prefer to call it, a very small per cent of our cases, 8%, have had, in addition to their confirmed atresia, fairly reasonably complete giant-cell transformation of the liver, and so presence or absence of giant cells, per se, even though it argues very much in favor of "hepatitis," does not completely rule out the existence of biliary atresia. We have found, I think, most interestingly, as Dr. Brent indicated, that there is a group of diseases leading to jaundice in early infancy which we just do not know anything about. There are several children who on repeated biopsy have no bile ducts at all, but excrete rose bengal and are getting well. We have no explanation for this. We strongly recommend that biopsy should be performed very early, preferably in the first few weeks of life. The precautions we use are those for bleeding tendencies and, practically, that is all. We use a transabdominal approach and have so far found it very satisfactory, provided that the liver is palpable.

DR. SYDNEY S. GELLIS, Boston: I just want to utter a word of caution. I think the success of the authors is very striking, but I would hope that it does not result in everyone poking at the liver for biopsy material. If you take very cooperative patients, such as dead babies, and do a punch biopsy and then a necropsy, you may be very horrified at what you will see in the liver. This procedure should be carried out by one person in a hospital and not be carelessly considered or used.

In our experience with atresia of the bile ducts, we have encountered little difficulty if exploratory operation is carried out at about 3 months of age, although I can see that a rare patient may have irreversible damage at this time. However, it is important to remember that operative success in biliary atresia is uncommon: In our last 30 consecutive patients with atresia, only 1 has proved to have a correctible lesion. On the other hand, patients with so-called neonatal hepatitis do poorly with surgery; hence our reluctance to explore too early. We prefer a biopsy under direct vision to punch biopsy, withholding careful exploration until the results of the biopsy have been obtained.

DR. A. ASHLEY WEECH, Cincinnati: I wish to make a confession. During more than 20 years of particular interest in the subject of neonatal jaundice, I have failed to see a single infant with an anomaly of the biliary system that could be corrected by surgery, even though the number of them explored in this way has been very large. The circumstances make me most sympathetic toward a technique that will help avoid unnecessary surgery, and I thank Dr. Kaye for his contribution.

May I also deplore the use of the phrase "confirmed atresia of the bile ducts," when what is meant is that bile ducts could not be seen at the time of surgical exploration. We are not alone in having observed the spontaneous recovery of

patients who had had an earlier operation at which the surgeon had stated that no bile ducts could be found at all. The point is that at this age period collapsed bile ducts may be so small as to be invisible to the naked eye.

May I also enter a plea for better history taking in some of these cases. It would be most interesting to have detailed knowledge of the color of the first meconium. In true atresia of the bile ducts the dark green pigment characteristic of normal meconium should be absent.

DR. ROBERT KAYE: In answer to Dr. Hsia's question, we have also tried the response to cortisone as a differential point between jaundice secondary to biliary atresia and that secondary to hepatitis. We were disappointed in its value very early, as we encountered patients with biliary atresia who showed pronounced falls in concentration of bilirubin in the serum. Ducci has noticed a similar response in adult patients with complete mechanical obstruction of the common bile duct. He has attributed this to decreased formation of bile pigments, as he has noted a concurrent fall in urinary excretion along with a decline in the serum concentration.

Dr. Sass-Kortsak asks particularly about our method of cholangiography. I want to emphasize that we leave the tube in place in the gallbladder, because not infrequently the operative cholangiogram is not entirely satisfactory. We have done as many as two postoperative cholangiograms in patients in an effort to visualize the right and left hepatic ducts, which is the difficult area in establishing complete patency of the biliary tract. In only one case have we failed to show a complete biliary tree in a patient whom we thought did not have biliary atresia. This was in the patient whom I have designated as having "probate hepatitis" and in whom we have never succeeded in getting the dye to pass into the duodenum from the common duct.

Dr. Brent's studies will, I am sure, add something valuable in the study of these patients. We have been impressed that patients with hepatitis may also have complete unremitting obstruction of the outflow of bile into the extrahepatic biliary tree. We have on a few occasions failed to obtain from the duodenum sulfobromophthalein injected intravenously in patients with hepatitis.

Dr. Newton commented on the value of operative biopsy in these cases. We employed needle biopsy because of the prevalent idea of the deleterious effects of operation on infants with hepatitis. It is possible that operative biopsy may prove to be safe and may ultimately become the preferred procedure.

In answer to Dr. Bauer's question, we have used the lateral transabdominal approach in practically all cases rather than the intercostal one. The patients have been restrained by adhesive strapping across the thighs and by a nurse holding the hips.

In reply to Dr. Gellis' comments, we were led in part to evaluate needle biopsy because of his work which tended to show unfavorable effects of exploration in infants with hepatitis and by reports in the literature of several hundred needle biopsies in infants with nutritional liver disease without serious untoward effects.

I appreciate Dr. Weech's comments. Another patient, not presented in the paper, came to us after a 10-month hospitalization in another institution. An operable obstruction of the common duct was found, but the patient's condition was so deteriorated that he died soon after laparotomy.

There is no doubt that cholangiography will usually give a more satisfactory indication of the biliary tract anatomy than entensive examination by exploration.

**Effect of Vitamin K and Naphthalene Metabolites on Glutathione Metabolism of Erythrocytes from Normal Newborns and Patients with Naphthalene Hemolytic Anemia.** W. H. ZINKHAM, M.D.,* and BARTON CHILDS, M.D.,* Baltimore. Introduced by Robert E. Cooke.

Erythrocytes from certain adults possess an intrinsic defect which makes them unusually susceptible to the hemolytic action of primaquine and certain other drugs. This defect is characterized by a low level of reduced glutathione (GSH) and a marked fall in GSH when erythrocytes are incubated with acetylphenylhydrazine (APH).

A similar defect was found in erythrocytes from four Negro patients who developed a severe hemolytic anemia following exposure to naphthalene moth balls. Of particular interest in this group were a mother and infant, both of whom manifested an acute hemolytic anemia in the immediate postpartum period. The mother had been smelling and nibbling naphthalene moth balls sporadically during the last trimester, and her infant was observed to be icteric at 8 hours of age. Microspherocytes and fragmented red cells were seen on smears of peripheral blood. During the first 30 hours of age the infant's hematocrit value fell from 43% to 31%, and the serum bilirubin rose from 6.0 to 22.0 mg. per 100 cc. At 36 hours an exchange transfusion was performed, and the infant did well thereafter.

When erythrocytes of these four patients were incubated with APH, naphthalene metabolites ($\alpha$- and $\beta$-naphthoquinone and $\alpha$- and $\beta$-naphthol), and menadione sodium bisulfite (Hykinone), a derivative of $\alpha$-naphthoquinone, there was a marked fall in GSH. This effect was observed in concentrations which failed to reduce GSH of normal erythrocytes. The abnormality in GSH metabolism

* By invitation.

of the infant's erythrocytes gradually disappeared during the first eight weeks of life, while that of the mother's red cells persisted.

Observations by others on the hemolytic effects of vitamin K in infants suggested that the GSH abnormality might exist in newborn babies. Accordingly, red cells from a series of 26 normal full-term Negro and white infants, 4 to 78 hours old, were incubated with APH, and there was a moderate to marked fall in GSH in all. Menadione sodium bisulfite in concentrations of 0.02 to 0.05 mg. per 1.0 cc. of whole blood produced a similar decrease in GSH. Substitution of adult for infant plasma before incubation with menadione sodium bisulfite did not alter the reduction of GSH.

The occurrence of a naphthalene hemolytic anemia in a newborn infant and the decrease of GSH of normal infants' erythrocytes after incubation with vitamin K indicate that red cells of newborns are susceptible to the hemolytic action of certain drugs. The relation of these findings to the development of hemolytic anemia and kernicterus in infants receiving vitamin K will be discussed.

Studies of the effects of APH, naphthalene metabolites, and menadione on GSH of erythrocytes from relatives of the patients with naphthalene hemolytic anemia were carried out. Other families, ascertained through persons whose erythrocytes reacted strongly to these agents, and who were found by screening a large unselected group of persons in the outpatient department, were similarly studied. All but one of the families containing one or more "reactors" were Negro, indicating a strong racial predilection of this characteristic. The distribution of reactors in these families indicated that the susceptibility to alteration in GSH metabolism and hemolysis by the agents used is genetically determined and is associated with the presence of a single dominant gene. In the case of the newborn infants, on the other hand, the incidence of positive reactors was many times that among the children and adults tested, suggesting that the defect in newborn infants reflects some metabolic immaturity, nongenetic in origin. Thus the susceptibility to poisoning by naphthalene as well as by certain allied drugs is a product of immaturity in the newborn infant, while in older infants, children, and adults it is an inheritable characteristic.

### Discussion

DR. WOLF W. ZUELZER, Detroit: This is truly a beautiful piece of work. It is intellectually very gratifying, because it really explains some problems which existed from the very beginning with respect to the clinical and hematologic sequels of naphthalene ingestion. At the start, when we first became aware of the relationship between naphthalene poisoning and hemolytic anemia, it was apparent that only a certain number among patients who had a definite history of naphthalene ingestion would develop anemia. Moreover, all of the patients seen in our clinic thus far with hemolytic anemia following naphthalene poisoning have been Negro children. I wonder if Dr. Zinkham will comment further on this racial factor later on. Our experience in this respect fits the very beautiful material he and Dr. Childs have described.

In the light of Dr. Beutler's findings on primaquine sensitivity in some 20% of Negroes, we assumed, like Dr. Zinkham, that the naphthalene susceptibility seems to reflect a biochemical defect and should have a genetic basis. We attempted in rather an amateurish way to do what Dr. Zinkham has so beautifully completed and shown us here. In our own clinic we tried to characterize the defect by the demonstration of Heinz bodies, which are in some way related to the failure of the glutathione protecting mechanism, and our test system included acetylphenylhydrazine, vitamin K, sulfisoxazole (Gantrisin), etc., added to red cells in vitro. Unfortunately, this method is not suitable for good quantitative studies, and we were unable to make satisfactory correlations. The chemical determination of gluthathione is, of course, a very much better method.

Using this method, we have done studies on the red cell glutathione content and glutathione stability in newborn infants, with results that are entirely confirmatory to those of Dr. Zinkham's. I might add that we were unable in our studies thus far to demonstrate any difference in the response of red cells to vitamin K in vitro between full-term and premature infants. These studies of the glutathione stability correlated well with the development of Heinz bodies. In contrast to our experience with vitamin K, which produced Heinz bodies and brought about a drop in red cell glutathione, we were able to produce Heinz bodies in red cells incubated with sulfisoxazole, but we have not as yet noted a drop in the glutathione level when cells were incubated with sulfisoxazole. This brings up the very interesting question as to what biochemical changes are related to the production of Heinz bodies. Most people regard these strictly as a degradation product of hemoglobin, and a close relation to the glutathione protecting mechanism has been assumed.

Just one note of clinical speculation. It is becoming more and more apparent, from studies such as these, that vitamin K preparations can be harmful, at least in large doses, to the newborn infant. Work such as has been reported during the past year on the coagulation mechanism of the newborn infant indicates that neither the prothrombin complex as a whole nor the components thus far measured are significantly influenced by the ad-

ministration of vitamin K to either mother or infant or both.

Taking these two facts together, we should begin to think seriously about abolishing the practice of routine administration of vitamin K, and above all we should reevaluate the claims that have been made for vitamin K in the prevention of so-called hemorrhagic disease of the newborn. With respect to the potential damage done by vitamin K, I should like to mention that we recently observed a pair of twins, one of whom had received substantial doses of vitamin K. This infant developed profound jaundice and his erythrocytes showed Heinz bodies, whereas the other twin, who had not received the drug, showed no jaundice and had no Heinz bodies or anemia.

Dr. Laurence Finberg, Baltimore: How does Dr. Zinkham apply his findings concerning vitamin K to routine nursery practice, particularly in the premature infant? Did I hear him suggest that vitamin $K_1$ might be a superior substance to use?

Dr. Lewis A. Barness, Philadelphia: I want to thank Dr. Zinkham for a very lucid presentation. I should like to ask him one question: That is, whether or not he did any hydrogen peroxide hemolysis on these cells. We have studied vitamin E-deficient red cells in rats by this method. We were also unable to demonstrate a relationship of vitamin E-deficiency hemolysis and glutathione.

Unidentified discusser: I wish to congratulate the authors on their excellent presentation, and I should like to comment on one phase of their rich material, namely, the part of the presentation dealing with newborn infants.

For the last seven years we have studied the activity of the red blood cells in vitamin E-deficient animals and in the newborn infant, just as Dr. Gordon and his group has done in Baltimore, and, (just limiting my remarks to newborns) we found the red blood cells of the newborn infant in general reactive to $H_2O_2$. This reactivity has been neutralized by vitamin E in vitro as well as in vivo, meaning that when vitamin E was given to the newborn infant the red blood cells became resistant to $H_2O_2$. With regard to vitamin K, it has been shown first by Dr. Moore in Cambridge, England, that the vitamin K or the K analogue hemolysis depends also on vitamin E deficiency, and with vitamin E given to animals or almost certainly given to infants, as is being done now, the vitamin K analogue hemolysis or vitamin K hemolysis can be prevented.

With regard to vitamin $K_1$, it perhaps will interest the audience that, according to unpublished studies of Dr. Gustafson in Sweden, in germ-free animals the menadione type of synthetic vitamin K preparations will not prevent vitamin K deficiency.

My question is, therefore, whether Dr. Zinkham feels that with vitamin E given to the newborn infant in vivo he would have prevented the hemolysis or even the drop of the glutathione in his APH test. As far as I understood it, he gave the vitamin E only to suspended red blood cells.

Dr. W. H. Zinkham: The comments of the discussers have filled in several gaps in our presentation, as well as focused attention on pertinent points which were omitted for lack of time.

In relation to Dr. Zuelzer's comment concerning the relation of racial background to the occurrence of a naphthalene hemolytic anemia, it was Dr. Zuelzer's report of this condition in Negroes several years ago that helped to stimulate our interest in this problem. In his paper, Dr. Zuelzer also referred to work by Smillie, of South America, who, after observing a hemolytic anemia in approximately 10% of negroes receiving $\beta$-naphthol for hookworm disease, suggested that there was some intrinsic abnormality of the red cells from these persons which made them especially susceptible to the hemolytic effects of $\beta$-naphthol.

The possibility of other racial groups having a similar defect in glutathione metabolism is now being explored. To date, 17 families containing one or more reactors have been surveyed. Fifteen of these families were Negro, and the remaining two were Greek, from the Isle of Rhodes. The latter two families were studied because one male child from each had developed a severe hemolytic anemia following ingestion of fava beans. Whether the frequency of this red cell abnormality is the same in Greeks as in Negroes has not been determined, but the transmission of the gene responsible for this defect followed a similar pattern in the two racial groups.

We, too, have found no decrease in GSH content of erythrocytes incubated with sulfisoxazole, even in final concentrations of 50 mg. per 100 cc. Since the naphthalene metabolites, rather than naphthalene, were the effective in vitro oxidants, sera from patients receiving sulfisoxazole and having sulfisoxazole levels of 10 to 15 mg. per 100 cc. were incubated with red cells from normal newborn infants and adults. Again no decrease in GSH was observed. Heinz body studies were not done on these preparations.

As for the occurrence of a hemolytic anemia in premature and newborn infants following administration of vitamin K analogues, we do feel that this is a cause-effect relationship, particularly if the infant has reacting red cells. Recently we observed a 5-day-old Negro boy who manifested a severe hemolytic anemia after receiving 10 mg. of menadione sodium bisulfite parenterally. Several months later this patient was shown to have reacting red cells. In newborns with nonreacting red cells, larger doses of vitamin K analogues may be necessary to effect hemolysis.

Whether vitamin $K_1$ is devoid of in vivo hemolytic activity can not be deduced from our in vitro studies. Since vitamin $K_1$ is suspended as an oil emulsion, the inability of this preparation to reduce GSH of erythrocytes may be related to its insolubility under the conditions of the experiment. On the other hand, Allison has shown that vitamin $K_1$ does not produce hemolysis in vitamin E-deficient rats, whereas other commonly used water-soluble vitamin K analogues will.

The relationship between vitamin E deficiency, glutathione metabolism, and vitamin K-induced hemolysis in the newborn infant is not known. In our experimental system addition of α-tocopherol to a final concentration of 1000γ per 100 cc. prior to incubation of infant's whole blood with menadione did not alter the reduction of GSH. Glutathione studies have not been done after the administration of vitamin E to the infants or their mothers.

**The Treatment of Paradoxical Hypertension and Necrotizing Arteriolitis Following Resection of Coarctation of the Aorta.** JEROME S. HARRIS, M.D.; W. C. SEALY, M.D.*; W. G. YOUNG JR., M.D.,* and H. A. CALLAWAY JR., M.D.,* Durham, N. C.

It is paradoxical that a successful operation designed to correct hypertension may lead to serious and even fatal hypertensive episodes. We have reported that two types of hypertension may occur unexpectedly following successful resection of an aortic coarctation. The first type begins in the immediate postoperative period and subsides uneventfully in several days. The second and sometimes fatal type is delayed in onset. It begins after the second postoperative day and is characterized by a diastolic hypertension that is significantly higher than the preoperative level. In some patients this condition is asymptomatic and subsides spontaneously in 12 to 14 days. Others may have poorly localized abdominal pain, anorexia, nausea, leukocytosis, and vomiting. In several cases these symptoms have progressed, in the absence of treatment, until abdominal wall spasm and severe tenderness appeared. X-rays showed segmental dilatation of the small bowel with retention of gas. There was also striking x-ray evidence of edema of the intestinal walls. In two cases abdominal exploration became necessary. Segmental areas of bowel wall necrosis were found. In one patient the lesion was so extensive that resection was impossible and death resulted. In the other case, a 4-year-old boy, the gangrenous area was resected and the child recovered. Microscopic study showed extensive medial necrosis throughout the vascular tree of the involved bowel. Similar changes were seen in the vessels of the abdominal wall and in the inferior epigastric artery. Autopsy in the first case showed extensive vascular necrosis involving only the vessels below the coarctation and none above this level. These changes were similar to those noted in experimental renal hypertension and may result from the sudden elevation of pressure in these vessels.

It is most important to recognize this syndrome in the early stages, since therapy can be life saving. At almost any time the progression of symptoms may be halted by the proper administration of antihypertension agents. Three children who developed hypertension and progressively severe abdominal pain with physical signs of impending serious bowel involvement have been treated with hypotensive agents (hydralazine and reserpine). There was a rapid fall in the hypertension and the abdominal pain, spasm, vomiting, and leukocytosis quickly subsided. Recovery was uneventful.

### Discussion

DR. J. N. ETTELDORF, Memphis: I wonder whether the authors correlated this syndrome in any way with the adequacy, or should I say inadequacy, of collateral circulation, and is there any relationship to the duration of the clamping of the aorta?

DR. JEROME S. HARRIS: There was no correlation between the occurrence of hypertension following operation and the extent of collateral circulation, the type of coarctation, or the duration of the operation. In one of the patients with severe postoperative hypertension the operation was very prolonged because the subclavian artery had to be used for the anastomosis; in the other patients, the operation was simple and uncomplicated—apparently no different from any of the other operations.

With regard to the question as to whether vascular pathology was present at the time of surgery, no abnormalities were noted in the tissues which were removed from some of the patients at operation. Further, in the patient who died, there were no lesions above the area of the coarctation. For these reasons, we doubt whether any of the vascular lesions existed at the time of operation.

**The Effect of Exercise on Left-to-Right Shunt of Blood Through a Ventricular Septal Defect, as Shown by Dye-Dilution Curves.** D. SHIRLEY MURRELL, M.B., B.S.,* and DONALD E. CASSELS, M.D., Chicago.

A left-to-right shunt in patients with a ventricular septal defect may diminish or increase with exercise. These findings have been correlated with pressure readings obtained at cardiac catherization.

Dye-dilution curves were obtained in the standard way, using a modified Woods ear oximeter and

* By invitation.

Evans blue dye in doses of 0.2 mg. per kilogram of body weight. A curve was taken at rest, with the patient lying down, and a second curve was obtained after exercise for three to five minutes.

Patients who had normal right ventricle and pulmonary artery pressures at cardiac catherization showed an increase in left-to-right shunt with exercise. The pressure gradient across the ventricular septal defect would increase in these cases with exercise, thereby increasing the flow through the defect. The arteriovenous shunt was found to diminish with exercise when right ventricular pressures were raised because of pulmonary hypertension or pulmonary stenosis.

In the normal lung the pulmonary artery pressure does not rise with exercise, in contrast to the systemic artery pressure. These pressure changes are reflected in the intraventricular systolic pressures and result in an alteration of the interventricular pressure gradient. When the right ventricular pressure rises concurrently with that in the left ventricle, the left-to-right shunt will not increase and may decrease. Pulmonary vascular changes associated with pulmonary hypertension cause an increase in resistance to blood flow, leading to raised pulmonary artery pressure when the cardiac output rises with exercise. It is suggested that pulmonary stenosis has the same effect on the right ventricle.

It would appear that in the high-pressure zones of the ventricles the primary fact controlling the shunt is the pressure gradient.

Increased rate of blood flow due to lowered muscle arteriolar resistance will have the effect of diminishing a shunt. This is seen in patients with interatrial septal defect whose left-to-right shunt diminishes with exercise, as reported by Hickam and found by us.

(The discussion of this paper is combined with the discussion of the following paper.)

**The Natural Transformation of Ventricular Septal Defects into Ventricular Septal Defects with Pulmonary Stenosis and/or into Tetralogy of Fallot: Clinical and Physiologic Findings.** BENJAMIN M. GASUL, M.D.*; ROBERT F. DILLON, M.D.,* and VLASTIMIL VRLA, M.D.,* Chicago. Introduced by HEYWORTH N. SANFORD.

In our experience isolated ventricular septal defects are the commonest type of congenital malformation of the heart. During the past ten years we have studied 342 patients with this malformation. Ninty-five of these have had cardiac catheterization studies, in addition to complete physical examination and phonocardiographic, angiocardiographic, and electrocardiographic studies.

The natural course of patients with ventricular septal defects is not definitely known. We accept the generally held opinion that some patients with ventricular septal defects develop findings of Eisenmenger complex, usually in the second or third decade of life. The autopsy records of our patients studied at Cook County Children's Hospital, Research Hospital of the University of Illinois, and Presbyterian Hospital revealed 27 infants up to the age of one year. Many of these infants died during the first few days or weeks of life. These records also revealed that during the past 10 years no autopsies have been performed on patients with ventricular septal defects between the ages of 1 and 15 years.

In common with other authors, we have repeatedly observed that infants with large ventricular septal defects manifest marked improvement in their symptomatology after their first year of life. In the early progress of our studies we found that 4 patients out of 15 who have had cardiac recatheterization revealed evidences of associated infundibular pulmonary stenosis, and 2 of these 15 patients revealed definite clinical and physiologic findings of tetralogy of Fallot.

In an attempt to explain these observations we have decided to combine our clinical follow-up examinations with cardiac recatheterization and angiocardiography, especially in those of our patients who have had their initial studies during their first year of life.

We believe that we have documented for the first time that some patients with ventricular septal defects develop in the natural course of this malformation associated infundibular pulmonary stenosis and/or evidences of tetralogy of Fallot. Slides demonstrating the salient clinical and laboratory findings, including pressure curves obtained from the right ventricle and pulmonary arteries in the first and repeat studies, were presented.

*Example of Salient Catheterization Findings in One Patient*

| | Age 11 Mo. (4/10/52) | Age 4 Yr. 9 Mo. (3/5/56) |
|---|---|---|
| Inferior vena cava | 8.97 | |
| Superior vena cava | 8.25 | 9.80 |
| Right atrium (upper) | 8.08 | 9.64 |
| Right atrium (middle) | 8.55 | Clotted |
| Right ventricle (inflow) | 10.98 | 11.82 |
| Right ventricle (outflow) | 11.80 | 12.32 |
| Pressure, right ventricle | 56/1 | 89/2 |
| Right pulmonary artery | 12.11 | 13.02 |
| Pressure, pulmonary art. | 30/16 | 20/5 |
| Peripheral art. $O_2$ sat. | 95.6 | 91.2 |
| | Index L./Min./ Sq. M. | |
| Calculated blood flows | (4/10/52) | (3/5/56) |
| Systemic | 3.15 | 3.23 |
| Pulmonary | 12.2 | 6.59 |
| Shunt (L-to-R) | 9.05 | 2.29 |
| | Over-all: R-to-L=0.25 L-to-R=2.04 | |

* By invitation.

### Discussion

DR. SAUL J. ROBINSON, San Francisco: I think that Dr. Gasul has presented documented work which seems to indicate that not only does the child or infant with an interventricular septal defect protect himself to survival by means of changes in the vasculature of the pulmonary arteries but, in addition, may protect himself apparently by an increase or a development of pulmonary stenosis in the infundibulum of the right ventricle.

I want to ask Dr. Gasul whether he feels, as do some others, that the large majority of the patients with ventricular septal defects take neither one of these two courses, but go on to a more benign and long-lived existence.

DR. FOWLER, New Orleans: About four years ago our group first reported the tetralogy of Fallot at exercise only, as we called it at that time, at the World Heart Conference in Washington. At that time we did not actually understand the growth and developments, so to speak, of this lesion. Only recently have we become aware of the phenomenon which was described today by Dr. Gasul and his associates, through two parallel experiences of our own.

One patient was a 1½-year-old child who had catheterization data showing evidence of a large ventricular septal defect with large left-to-right shunt equal to systemic pressure. There was no pulmonary gradient whatsoever in this particular case. Clinically the child was doing poorly, but about two years later, following improvement clinically, he was recatheterized for consideration of surgery. At this time he was found to have developed marked pulmonary stenosis, with right ventricular pressures still equal to the systemic pressure, but the pulmonary pressure was now only the upper limit of normal.

The second child was a 4½-month-old infant who was in failure with a large ventricular septal defect and marked pulmonary hypertension, with perhaps just a suggestion of a pulmonary gradient. This child was recatheterized and was studied surgically about two months later and was found to have developed a certain amount of pulmonary stenosis, with approximately a 30 mm. gradient, during this two-month period. There was also, interestingly, some narrowing of the annulus of the pulmonary valve, and there was slight poststenotic dilatation of the pulmonary artery which was noted at the time of surgery. We now believe that pulmonary stenosis of infundibular type may develop postnatally in a variety of malformations, including pulmonary valvular stenosis, and we think that possibly we have seen this happen in a case of patent ductus arteriosus with pulmonary hypertension initially. The common denominator is right ventricular hypertension, and anatomically caused, we believe, by the same mechanism that Dr. Gasul has suggested, namely, progressive hypertrophy of the right ventricle inflow, so that eventually the infundibular type of obstruction may be encountered.

The problem that I still think has to be solved is the question that Dr. Robinson has already raised and which I hope Dr. Gasul and others will be able to give us some further data on eventually, and that is just how many of these cases will go in which direction.

DR. GEORGE S. HUSSON, Syracuse, N. Y.: I should like to ask Dr. Gasul how many of these patients had enlarged hearts when the diagnosis of tetralogy of Fallot was made. At Cincinnatti last year, three patients with so-called tetralogy of Fallot with enlarged hearts were reported by Blount. I wonder whether these patients may not also represent transformations when these patients are seen in early childhood. I wonder if Dr. Gasul would comment on this point.

DR. HOWARD A. JOOS, Los Angeles: The authors of the two preceding presentations must be complimented on their interest in the natural history of patients with ventricular septal defects. Our internist colleagues frequently wonder why they encounter fewer ventricular septal defects among adults. Dr. Gasul's observations, in particular, may suggest some of the reasons.

Dr. Murrell may wish to comment further on the pitfalls in interpreting hemodynamic information too rigidly. The determinants of ventricular outflow with a ventricular septal defect may be more complex than simple comparisons of flow, pressure, and resistance in pulmonary and systemic circuits. Our patients often seem less predictable than our mathematics.

It is even possible to suggest a hemodynamic situation with fixed pulmonary vascular resistance where exercise might increase pulmonary blood flow and left-to-right shunt by increasing the gradient of pressure across the defect or by otherwise altering the physiology of the contracting ventricle in favor of such a change. The prognosis with or without surgery might still be poor, and Dr. Murrell's dilution curves might be misleading. We must remain cautious in interpreting either flow or pressure when we understand the dynamic situation incompletely.

DR. PAUL ADAMS JR., Minneapolis: What is the oldest age at which Dr. Gasul feels this transformation can occur? We have noticed this in one or two patients, but it has always been pretty obvious by the time a child was 2 years of age, and I am wondering how long we need to wait for this transformation. Can we say that if a child shows signs of ventricular defect at 4

years of age he will no longer be likely to acquire a pulmonary stenosis?

DR. ROBERT J. MCKAY, Burlington, Vt.: I should like to repeat the same question that Dr. Adams asked, because during the past year we believe we have seen a child whom we first saw at the age of 6 and catheterized, who now at the age of 7 appears to have undergone this transformation.

DR. DUNNE, Vancouver, B. C., Canada: I have been particularly interested in Dr. Gasul's very beautiful exposition of the gradual rise in the right interventricular pressure in these cases of ventricular septal defect. I presently have under my care an infant aged 3 months, who appears to have a ventricular septal defect and is in failure. I should be very interested to have Dr. Gasul's comments on the possibility of therapeutic applications of the developments that he has described. I believe that there is an operation presently being developed in which a partial pulmonary stenosis is caused artificially in infants with the situation where there is a ventricular septal defect and failure, and I should be glad to have Dr. Gasul's comments on this operation.

DR. GEORGE S. HUSSON, Syracuse, N. Y.: I should like to ask Dr. Murrell whether she has studied the effects of reversal of shunts by means of indicator-dye-dilution techniques under conditions of mild hypoxia in these patients.

DR. NELSON K. ORDWAY, Chapel Hill, N. C.: I wonder whether the transformation described by Dr. Gasul can occur much earlier? I wonder whether this might be a more reasonable explanation than the alleged closure of the ductus for the rapid worsening that occurs clinically in patients born with the tetralogy of Fallot.

DR. D. SHIRLEY MURRELL: In reply to Dr. Joos' remarks, I quite agree with him; the factors causing blood flow through a ventricular septal defect appear complex. I think that the easiest way to examine them is to first consider the pressure differences, and then the differences in resistance to flow from the right and left ventricles. If there is a pressure gradient which alters at the ventricular level, there will be some increase or decrease in flow through a septal defect, depending on the direction of change.

We should like to be able to calculate the amount of exercise which the patient does, but this is not really practicable in children, as they will not always exercise at a constant rate. The average amount of exercise done was 1.7 ft-lb. per second; the range, 1.2 to 2.4 ft-lb. per second. The raising of the systemic blood pressure by exercise was not always constant either, and, as we showed in the penultimate slide, this is of great importance if this test should be used in trying to differentiate those patients who have pulmonary hypertension from those who have not.

Dr. Husson's question. No, we did not study patients who had induced mild hypoxia. Our patients throughout the tests were breathing 100% oxygen, and so this factor was constant and could be excluded as a cause of change in blood flow.

DR. BENJAMIN M. GASUL: Dr. Robinson asked about the natural course of patients with ventricular septal defects. As I have stated previously, we can not give a definite answer to this question. However, it is important to emphasize that according to our autopsy records and to the reports in the literature, these patients do not die during the pediatric age once they pass the age of one year. Therefore, there does not seem to be any particular hurry in advising an operation, especially since the operative mortality rate at present is very high. How many of these young patients with ventricular septal defects undergo a natural transformation is at the present time not known.

I am glad that in New Orleans they have also found this natural transformation of ventricular septal defects into ventricular septal defects with pulmonary stenosis.

Dr. Husson's question regarding patients with tetralogy of Fallot with definite cardiac enlargement is an interesting one. I believe that some patients with tetralogy of Fallot and little or no cyanosis originally have had a large ventricular septal defect only and later on developed infundibular stenosis due to hypertrophy of the crista supraventricularis and the septal and parietal bands. If this hypertrophy is marked, a definite and marked gradient develops between the right ventricle and pulmonary artery, and this may lead to a bidirectional shunt and thus to all the manifestations of tetralogy of Fallot.

Dr. Joos wishes to know why the internists do not see many patients with ventricular septal defects. A few of these patients, of course, die during the first year of life. Fortunately, early death from uncomplicated ventricular septal defects is nowadays rather uncommon, particularly if these patients are treated with antibiotics and digitalis. A few of these patients develop Eisenmenger's complex later on in life, and some patients, later on present themselves with either tetralogy of Fallot or ventricular septal defects and infundibular stenosis.

There is a question regarding the advisability of surgical intervention on young infants with large ventricular septal defects. Our surgeon at the Presbyterian and Cook County Children's Hospitals and I are rather conservative in advising an operation on these infants. We have had only six patients operated on for ventricular septal defects. The reports from various clinics in our country and in Canada reveal a very high surgical mor-

tality. In one of the outstanding clinics, of 12 infants who were operated on for ventricular septal defects 11 died and the 12th patient is not doing well. Of six patients in another clinic all died. Theoretically, all patients with ventricular septal defects should have these defects closed, and it is possible that in the future, when the surgical mortality will have been markedly lowered, we are going to advise operations on all patients with ventricular septal defects just as we do now with uncomplicated patent ductus arteriosus. At the present time, however, we usually advise against surgical intervention on patients with ventricular septal defects.

Dr. Paul Adams questions regarding the age at which this natural transformation usually takes place. From our preliminary work it appears that if a natural transformation is going to take place it probably appears at an early age. All of us who are interested in this subject have observed a number of very young patients with all the clinical evidences of large ventricular septal defects who later on develop a diminished second sound over the pulmonary area. However, in order to document this natural transformation, these patients must have cardiac catheterization at an early age and later on must undergo a cardiac recatheterization.

The question regarding the advisibility of surgical intervention in a critically ill 3-month-old infant with a large ventricular septal defect is a difficult one to answer. Personally, I would be opposed to advising an operation. The mortality on these very young infants, even in the hands of the two surgeons who are the pioneers in this field, is still very high. Regarding this particular 3-month-old infant, I would at first make sure that there are no associated congenital malformations. In our experience, most infants with large ventricular septal defects who are treated with antibiotics and proper dosages of digitalis and who do not improve usually have other associated lesions. These infants improve remarkably after their first year of life, even though they still have a large left-to-right shunt at the ventricular level.

A question was asked as to whether the surgeon should create a pulmonary stenosis in these patients. Dr. Dammann suggested these operations a few years ago for some patients with large ventricular septal defects. We have had no experience with this artificially created pulmonary stenosis, and I do not know whether it should be performed in this particular case.

Finally, the last question, I believe, referred to the possibility of patients manifesting evidences of tetralogy of Fallot at birth having had pure ventricular septal defects at some early stage of their fetal development. I wish to emphasize that it was not our intention to suggest that all patients with tetralogy of Fallot, or even the majority of these patients, manifested at one time only evidences of ventricular septal defects.

## Papers Read by Title

**Composition of Pediatric Practice in the Antibiotic Era.** LEO J. GEPPERT, M.D.,* Washington, D. C. Introduced by Harry Gordon.

Mortality statistics are now generally available and are as accurate as is possible with current autopsy rates. Morbidity statistics, however, are almost nonexistent. The relative stability of the pediatric population of a large permanent Army post provided an opportunity to collect such data from a cross section of American persons. Complete medical care in all specialties was provided for eligible dependents of military personnel. This study is an analysis of the diseases treated per 10,000 children in the population—not an exact record of the disorders afflicting 10,000 consecutive children.

From a pediatric population of 10,000 children there were a total of 272,750 visits to the pediatric outpatient clinic in a period of 10 years. Ninety thousand of these visits were well-baby conferences and included 75,000 immunizations. Over 300,000 telephone calls were completed. There were 112,750 outpatient visits because of original illness, with 70,000 return clinic visits. These patients received a total of 93,000 therapeutic injections, chiefly of penicillin. Nine thousand of these patients (one admission per 12 illnesses) were admitted to the hospital. The average hospital stay was 10.2 days (acute illness, 5.3 days). There were 420 deaths between birth and 10 years of age, or 4.2%. Half of these were neonatal and half pediatric deaths. The autopsy rate was 95%. This clinical experience represents a horizontal view of a lifetime of pediatric practice in the present decade.

The diagnoses were catalogued according to the International Nomenclature of Disease. The index numbers of the diagnostic code were then reversed to give etiology precedence over topography. The number of diagnoses were then greatly reduced by consolidating as much as possible hundreds of minor topographical divisions. The total number of each disease was then recorded as incidence from birth to age 10 years per 10,000 children, or the incidence of 100,000 per year.

Eighty-four common diseases accounted for 95% of office visits, 76% of hospital admissions, but only 13% of the deaths. Four hundred fifty relatively rare disorders comprised less than 5% of outpatient diagnoses and only 24% of hospital admissions but accounted for 87% of neonatal and pediatric deaths. Log graphs have been prepared to illustrate the numbers of outpatients, inpatients,

* By invitation.

and neonatal and pediatric deaths for each disease per 100,000 pediatric population per year.

**Evaluation of the Physical Fitness of Older Children Using the Bicycle Ergometer.** LEONARD M. LINDE, M.D.*; FORREST H. ADAMS, M.D., and EDUARDO BORDA, M.D.,* Los Angeles.

Data obtained for adolescent boys were much more uniform and predictable than for girls of the same age group. Vital capacity in boys correlated with age and weight, while in girls height seemed to be the determining factor.

*Relation of Age, Weight, Height, and Surface Area to Pulse Rate After Exercise and Relation of Age to Surface Area*

| | Pulse Rate at 4 Min. | | | | Surface Area, Sq. M., Mean±S.D. | |
|---|---|---|---|---|---|---|
| | Boys | | Girls | | | |
| | Cases, No. | Mean±S.D. | Cases, No. | Mean±S.D. | Boys | Girls |
| Age, yr. | | | | | | |
| 11 | .. | .. | 10 | 175±17 | .. | 1.34±0.10 |
| 12 | 20 | 153±13 | 22 | 174±12 | 1.41±0.14 | 1.47±0.15 |
| 13 | 21 | 141±11 | 17 | 169±14 | 1.54±0.17 | 1.49±0.12 |
| 14 | 19 | 135±13 | 21 | 168±15 | 165±0.14 | 1.58±0.16 |
| 15 | 4 | 133±3 | .. | .. | 1.69±0.11 | .. |
| Weight, lb. | | | | | | |
| 78-120 | .. | 148±14 | .. | 176±11 | | |
| 121-190 | .. | 132±15 | .. | 165±9 | | |
| Height, in. | | | | | | |
| 55-62 | .. | 147±11 | .. | 175±11 | | |
| 63-74 | .. | 139±13 | .. | 169±14 | | |
| Surface area, sq. meters | | | | | | |
| 1.0-1.5 | .. | 149±14 | .. | 176±14 | | |
| 1.51-2.0 | .. | 135±15 | .. | 165±14 | | |

Originally it was hoped that the pulse response to exercise might distinguish normal and cardiac patients. The data demonstrate that the variation within each group is often greater than the difference between the groups. The response of compensated cardiac patients fell into the wide normal variation for their age, height, and weight. Further studies are now under way in the preadolescent age group to see whether the results obtained here are merely a reflection of the physiologic instability of adolescence.

**Behavior of Young Children Under Conditions Simulating Entrapment in Refrigerators.** KATHERINE BAIN, M.D.; MARION L. FAEGRE, B.A.,* and ROBERT S. WYLY, B.S.E.,* Washington, D. C.

Each year a number of young children die of suffocation as a result of being trapped in refrigerators. The National Bureau of Standards, in response to a Congressional request, undertook to assist the refrigerator industry with performance criteria for inside release devices. Since the effectiveness of such devices will depend not alone on engineering design but also on child behavior, the Children's Bureau assisted in designing a study in which children served as subjects, though so protected as to minimize psychological damage.

A test enclosure, resembling a child's playhouse, with inside dimensions of the average household refrigerator, was equipped to record the force exerted by the child and his behavior while in the dark through the use of infrared movies and sound tape records, plus a running account made possible by infrared illumination. If the child who failed to release himself promptly became disturbed, the observer opened the door.

Two hundred one children, aged 2 to 5, equally distributed by age and sex, were tested on six devices, including two developed in the course of this experiment as the result of observation of behavior. Success in escaping was affected by type of device, age, weight, and height of the child (but not the sex) and by the educational level of the parents, a higher rate of success being associated with fewer years of total parent education.

The wide range in behavior shown by children in reacting to entrapment was striking. Three major types of behavior were observed: (1) inaction, with no effort or only slight effort to get out (24%); (2) purposeful effort to escape (39%); (3) violent action both directed toward escape and undirected (37%). Age was not a factor in determining which children would be inactive. But, for those who reacted with move-

* By invitation.

ment, purposeful effort without violence increased steadily with age; violent activity decreased. Lack of success was associated with both inaction and violent activity; only 32% who displayed violent behavior got out, in contrast to 86% of those who went about the job quietly.

About 28% of the children made no outcry (6% of the 2-year-olds and 50% of the 5-year-olds). Some children had curious twisting and twining movements of the fingers or clenching of the hands. Where appropriate 61% pushed. When presented with a gadget that could be grasped, some (18%) pulled, a few (9%) pushed, but 40% tried to turn it like a door knob.

Time in the box was short for most children. Three-fourths were out in less than 3 minutes; one-third of these in less than 10 seconds. One-third of the children emerged unruffled; about half were upset but could be comforted easily, and a small group (11%) required some help in calming down. A follow-up study of these children to detect presence or absence of emotional disturbance is in process and will be reported.

Forces exerted by the children for whom such records were obtained ranged up to 29 lb., increasing from an average of 13 lb. at 2 years to 21 lb. at 5 years.

Data from these experiments proved valuable in developing standards for release devices (as required by Public Law 930), which are expected to be effective for self-release by a large percentage of, but not all, entrapped children.

This study has confirmed the hypothesis that the development of child protection devices must include behavioral as well as engineering research. Experiments can be designed, using children as test subjects, that reduce trauma to a minimum.

**A One-Year Controlled Study of the Effect of Low-Phenylalanine Diet on Phenylketonuria.** RICHMOND S. PAINE, M.D.,* Boston; KARL V. QUINN, M.D.,* Wrentham, Mass.; HANS MAUTNER, M.D.,* Wrentham, Mass., and DAVID Y-Y. HSIA, M.D.,* Chicago. Introduced by RANDOLPH K. BYERS.

The study included 24 phenylketonuric patients divided into pairs, comparable as to age, intelligence, and length of institutionalization. Twelve of the twenty-four patients were children, from the age of 3 years upward, and twelve were adults. Of the paired patients, one selected by lot received a low-phenylalanine casein hydrolysate as the protein component of his diet and the other, a control hydrolysate identical in appearance and flavor but containing all amino acids in the usual proportion. Also available for comparison are five unpaired patients aged 2 to 60, all receiving low-phenylalanine diets in the same institution, and five others aged 6 months to 16 years receiving the diets as outpatients.

Regular determinations of plasma phenylalanine and urine phenylpyruvate are essential and were made throughout the year's time. Chemical control is more difficult in institutional than in a home setting, and up to six months may be required to obtain normal plasma phenylalanine levels in adults and older children. Close clinical observation is also essential, and malnutrition, based chiefly on refusal of food, was a considerable problem. Secondary rises in plasma phenylalanine in previously well-controlled patients may occur in the presence of inadequate intake of calories or protein.

Only one of the paired experimental patients, a girl 3 years of age (and no control patients), showed significant increase in intelligence. An unpaired boy 2 years of age also improved on the experimental diet. Three outpatients, all started on the diet at the age of 3 years or under, also probably have improved, but these cases require more caution in interpretation. Significant change in intelligence, occurring only in the youngest patients in the study, suggests that improvement in intelligence will probably be confined to children under 4 years of age at the time the diet is begun. Older patients on the special diet showed significant changes, as compared with controls, in skin condition, hair color, behavior, and, to a lesser degree, in electroencephalograms. These changes are considered insufficient to warrant placing them on a difficult and potentially dangerous diet, however.

**Epileptic Equivalents in Children.** C. HARRISON SNYDER, M.D.* Introduced by RALPH V. PLATOU.

This paper points out the value of EEG in the study of a variety of nonconvulsive disorders in childhood. Among these are recurrent headache, abdominal pain, dizzy spells, "cyclic" nausea and vomiting, nightmares, and even recurrent fever. Six cases are reported in detail with their EEG's described and illustrated, to show that these symptoms may be manifestations of cerebral dysrhythmia and may respond favorably to anticonvulsant therapy.

It is believed that such cases represent true epilepsy, but in the absence of frank convulsive seizures I prefer to term the attacks "epileptic equivalents." Others, whose works are cited, have reported similar cases under diverse labels, including "masked epilepsy," "abdominal epilepsy," and "abdominal migraine."

Finally, a syndrome resembling neurasthenia, and often suggestive of rheumatic fever, is described in three children who were found to have abnormal EEG's and responded favorably to hydantoin therapy. These children presented severe personality disturbances. They would whine and cry and

* By invitation.

timidly cling to their parents. They complained of numerous vague pains and aches in the legs, abdomen, or head. Frequently they were found to have temperature elevations as high as 102 F. Previous diagnoses of rheumatic fever, appendicitis, or chronic tonsillitis had been made, but no treatment had helped them. After electroencephalography unmasked the basic cerebral disorder, therapy with hydantoinates brought striking relief, with dramatic improvement in behavior and disposition.

Caution is recommended in the interpretation of minor abnormalities of the EEG and in the evaluation of the effects of therapy, the possible placebo value of medication being kept in mind. With these reservations, it is believed that the EEG can be a useful tool in the study of a variety of paroxysmal complaints or personality disturbances in children.

**Falling Hematocrit Value in the Premature Infant as a Sign of Intraventricular Hemorrhage.** WILLIAM A. BLANC, M.D.*; GARRISON RAPMUND, M.D.,* and WILLIAM A. SILVERMAN, M.D.,* New York. Introduced by RUSTIN MCINTOSH.

The hematocrit ratio was obtained daily, for at least three consecutive days, in 142 premature infants during the first week of life. The values were determined on venous blood by a micromethod. Twenty-three babies died and were autopsied. In 119 survivors the over-all mean value was 51.4±8. The daily elevations and drops remained within one standard deviation around the mean with a few exceptions, in spite of variations in environment, diet, and therapy. In any given surviving patient successive values remained at the same general level whether the first value was low or high. The means of all data in survivors and in infants who died did not differ significantly. These groups had comparable sex distribution, but mean birth weight was significantly lower in the autopsy series.

Marked differences in hematocrit values and variations were observed when the autopsy group was divided into cases with (Group A) and without (Group B) intraventricular hemorrhage (IVH) for comparison with the survivors (Group C). The distribution of pathological findings other than IVH showed no significant difference. Group A patients showed a greater mean drop in hematocrit from starting level, and reached a lower mean level, than did those of Groups B or C; these differences were highly significant. Between Groups B and C there was no significant difference in these respects. In all three series the mean day of maximum drop was Day 4. These results indicate that IVH may be of such magnitude as to be reflected in the hematocrit level. Actual measurements at autopsy confirmed this point. Pulmonary hemorrhage was associated with IVH in four cases and may have been a contributing factor in the hematocrit drop.

A significant difference in the mean survival time after the maximum drop was evidenced (Group A=0.67±1 day; Group B=8±6 days). The short interval in Group A between hematocrit drop and death suggests a causal relationship. This is of interest, since the immediate cause of death is difficult to determine in most premature infants presenting with multiple pathological findings. The association of IVH with a sudden hematocrit drop observed after a "free interval" supports the anoxic etiology of IVH as opposed to obstetrical trauma. The occurrence of a large proportion of intraventricular hemorrhages after the first day of life has been confirmed in a review of 230 cases in 994 consecutive autopsies of newborns.

Serial hematocrit determinations as a diagnostic test of IVH might permit consideration of therapeutic measures. It might also help to clarify the role of IVH in neurological disorders of infancy.

**The Decline of Rheumatic Fever: Average Recurrence Rates of Rheumatic Fever Among Seven Hundred Eighty-Four Children for Twenty-One Consecutive Calendar Years (1936-1957).** MAY G. WILSON, M.D.; WAN NGO LIM, M.D.,* and ANN MCA. BIRCH, M.D., M.P.H.,* New York.

Several studies in Great Britain, Canada, and the United States have reported a decline in morbidity and mortality of rheumatic fever. This downward trend is considered to have antedated the antibiotic era. The majority of investigators were cognizant of the limitations and difficulties inherent in evaluation of epidemiological data for rheumatic fever. Some of the influential factors which were considered to have contributed to the apparent downward trend were more accurate differential diagnoses, the control of infectious diseases, and better maternal care. Many of the more recent reports stress the role of antibiotic therapy.

In a previous study, age-specific recurrence rates for the years 1916-1940 were presented. In addition, recurrence rates for 12 consecutive calendar years (1924-1936) were found to reveal no significant time trend. To determine whether there has been any change in the past 20 years, the following investigation was undertaken.

The recurrence rate of the major manifestations of rheumatic fever was calculated for the years 1936-1957. This study included 784 children who have been under medical supervision at The New York Hospital children's cardiac clinic. Age-specific recurrence rates for ages 2 to 20 and average age-adjusted recurrence rates for successive calen-

* By invitation.

dar years were calculated. Analysis revealed that the age-specific recurrence rates for the entire period were not significantly different from those of the previous study. However, a significantly lower age-specific rate was obtained for ages 6 to 10 after 1950. Preliminary analysis of the age-adjusted rates for the 21 consecutive calendar years revealed fluctuations at specific years. There appeared to be a slight downward trend after the year 1940. The various factors which must be considered in interpreting these findings will be discussed.

**Studies in the Etiology of Chronic Rheumatic Fever.** CARL J. MARIENFELD, M.D.*; GEORGE SCHEFF, M.D., Ph.D.*; ELOISE HACKETT, B.S.,* and DANIEL JONES, Ph.D.,* Chicago.

The indirect causation of acute rheumatic fever by the Group A $\beta$-hemolytic Streptococcus appears to have been amply documented. The continuation and progression of the cardiac involvement in a certain percentage of children despite adequate antibiotic therapy remains unexplained.

The possibility that a Streptococcus of differing antibiotic resistance may potentiate or continue the disease process originally invoked by the Group A Streptococus has never been adequately eliminated. The work of Wasserman and Westphal, Cecil, Small, and Birkhaug would appear to indicate the presence of such an organism in the blood of some patients with rheumatic fever.

It was therefore determined to seek again for an organism related antigenically or otherwise to the Group A Streptococcus which would be capable of inducing or maintaining rheumatic fever in children.

As a first step in this project we have cultured the blood of over 500 patients. These children are divided into those with rheumatic fever, those with other infections, and normal children.

Our results show a highly significant number of positive streptococcal cultures in patients with rheumatic fever as compared with the controls. The organism is similar in all cases. Its preliminary identification will be discussed. Its significance in the pathogenesis of rheumatic fever remains to be determined.

**A Surgical Cardiac Emergency—Pulmonary Atresia or Severe Stenosis in the Young Infant.** R. L. FOWLER, M.D.*; H. M. ALBERT, M.D.,* and ROSALIND NOVICK, M.D.,* New Orleans. Introduced by NELSON K. ORDWAY.

This report defines the status of isolated pulmonary valvular atresia or pinpoint stenosis (with patent foramen ovale) as a cardiovascular emergency occurring as early as the first 48 hours of life. Evidence is presented that this lesion may be diagnosed accurately and alleviated by prompt surgical intervention. Available information on this problem is meager for infants and nonexistent for neonates.

Eight cases ranging in age from birth to 11 months form the basis of this communication. The clinical picture, while somewhat variable, was characteristic. All children were severely cyanotic, showing, in the six cases studied, right-to-left shunts (through the patent foramen ovale) of 50% to 83% of the systemic venous return to the heart. Murmur was not characteristic, being absent or very faint in three and nonspecific in the remainder. Cardiac enlargement was uniformly present, slight in the newborn infants but striking in those surviving for a few months. Other features included dyspnea, lack of splitting of the second sound at the base, evidence of right ventricular failure, and faint diastolic pulsation of the liver—a highly characteristic sign, as indicated by its presence in seven of the eight cases.

Fluoroscopy and chest films showed enlargement of right atrium and ventricle with markedly diminished pulmonary vascularity. Prominence of the outflow tract of the right ventricle just below the pulmonary arc was noted in some cases. Electrocardiograms usually showed prominent P waves in Lead II, right ventricular hypertrophy, and/or right bundle branch block, but in one child (with a complicating Ebstein's abnormality) slight left ventricular predominance was noted. Cardiac catheterization in two cases was of value, but the other children were considered too sick to undergo this procedure. Systolic pressure in the right ventricle was elevated to the systemic level in one and was much higher than systemic in the other.

Six children were submitted to surgery. All survived the procedure except a 3-month-old infant with Mongolism who developed irreversible cardiac arrest during valvulotomy. Two infants died, of postoperative aspiration of vomitus and progressive cardiac failure, respectively, a few hours after completion of the procedure, and were found at autopsy to have a complicating Ebstein's malformation. One infant, who had clinical evidence of an associated patent ductus arteriosus, died unexpectedly on the second postoperative day. Autopsy permission was not granted. Two infants operated on at 96 hours and 26 days of age survived and appear to be doing well. The two children not operated on died at 8 days and 10 months of age.

The most important surgical consideration is speedy opening of the valve. When the chest is opened cardiac action rapidly deteriorates. The heart is very cyanotic, and the right ventricle is distended. Pulmonary artery is well formed but collapsed. A rapid valvulotomy is carried out with the Potts' valvulotome, and an almost immediate

* By invitation.

and striking improvement occurs in the patient's condition.

Results in pulmonary valvular atresia are not satisfactory but give promise of improving if diagnostician and surgeon collaborate in handling these cases on a top-priority emergency basis.

**Studies on Dogs with an Artificially Created Ductus Arteriosus and a Proximally Placed Coarctation of the Aorta.** HORACIO PADILLA, M.D.*; THOMAS FERGUSON, M.D.*; DAVID GOLDRING, M.D.*; M. R. BEHRER, M.D.*; A. F. HARTMANN JR., M.D.*; W. A. THOMAS, M.D.,* and H. A. HUMPHREY, M.D.,* St. Louis. With the technical assistance of CHARLES CRAWFORD. Introduced by ALEXIS F. HARTMANN SR.

We have been impressed by the high mortality rate of infants born with coarctation of the aorta proximal to a patent ductus arteriosus. When, however, these congenital defects occur singly, the threat to survival is not so serious. It has been noted in some of these infants with the combined defects that there may be reversal of flow through the patent ductus. The explanation for this is not entirely clear. We thought, therefore, it would be of interest to produce these defects artificially in dogs and make physiological studies of the altered hemodynamics.

The following experiments were carried out: Group I: Seven adult dogs were prepared with a fistula between the left pulmonary artery and aorta. Proximal to this defect a slowly developing constriction of the aorta was initiated. Group II: Eight adult dogs were prepared with an artificially created ductus arteriosus alone. Group III: In these adult dogs a slowly developing aortic constriction was started distally to the origin of the left subclavian artery.

All dogs had initial baseline studies and subsequent observations at periodic intervals until death. These studies included pressure determinations and blood oxyyen saturation of both the right side and systemic circulations. Radiographic and electrocardiographic studies were also included, and, after death of the animals, appraisal of the pathologic anatomical changes was made.

The results revealed that the dogs in Groups II and III lived from five to nine months and, although all developed varying degrees of cardiomegaly, they all did comparatively well when compared with the dogs in Group I.

In contrast, the dogs in Group I lived only from 13 to 56 days, and all died in congestive failure. Thus, as in infants, the combination of coarctation of the aorta and a distally placed patent ductus arteriosus is incompatible with survival of more than one to two months. All dogs in this group showed marked dilatation and hypertrophy of both ventricles. The intimal changes in the pulmonary arteries and arterioles, however, were surprisingly minimal. Although all dogs developed marked right ventricular and pulmonary arterial hypertension, none demonstrated a reversal of blood flow through the patent ductus arteriosus.

The significance of these findings is as follows: 1. The defects may have to be produced in very young animals and persist for a longer time than the above experimental period for anatomical changes to appear in the pulmonary arterioles. 2. These experiments suggest that the surgical obliteration of a patent ductus arteriosus in babies born with coarctation and patent ductus arteriosus may be a life-saving temporizing procedure.

**Physiologic Changes with Age in Ventricular Septal Defect Before and After Surgery.** PAUL ADAMS JR., M.D.*; RAY C. ANDERSON, M.D.*; PETER ALLEN, M.D., F.R.C.S.(C),* and C. W. LILLEHEI, M.D.,* Minneapolis. Introduced by JOHN A. ANDERSON.

The "natural history" of ventricular septal defect has recently become of greater interest, since it is now possible to correct these malformations by intracardiac surgery. This report deals with 30 patients having ventricular septal defect who have had two successive catheterizations at intervals varying from one to eight years apart prior to intracardiac surgery. There were five patients who showed a distinct fall in their measured pulmonary artery pressures over the span of years between catheterizations. The physiologic measurements of these patients taken as a group show a fall over the average of two years in total pulmonary resistance from approximately two and one-half times normal to one and one-half times normal. The pulmonary flow per square meter of surface area fell during the same interval. The reason for this change in a small number of patients is obscure. It is possible that it might represent measurement errors, since the studies were performed at various centers; or possibly, a decrease in the relative size of the ventricular septal defect compared to the over-all size and growth of the child, thus, creating relatively greater resistance to a left-to-right shunt. The second group consists of 12 patients who showed very slight changes in their mean pulmonary artery pressure over an average length of time of four years between studies. When averaged, the pulmonary and systemic flow per meter squared remained essentially unchanged over this four-year span. The total pulmonary resistance decreased with growth as measured by surface area, as would normally be expected. The pulmonary flow in cubic centimeters per second increased with increasing surface area of the patient, as would be expected, so that the mean pulmonary artery pressures remained unchanged.

* By invitation.

Thirteen patients, however, showed definite signs of increasing pulmonary artery pressures over the years and confirmed the clinical impression that in many instances this is a severely progressive malformation. Three of these patients had essentially normal mean pulmonary artery pressures when first studied, indicating a "latent" period at least up to 9 years of age in two of the cases. The remainder of the patients, however, had noticeably elevated pressures when first seen, and these progressively increased over the years between the studies. Lung biopsy or autopsy tissue was available from six of these patients, five of whom have shown intimal proliferation of the small pulmonary arterioles of severe degree. Total pulmonary vascular resistance increased only slightly on the average over the three years, but, when compared to normal values obtained in our laboratory, this represented an increase from twice normal to over three times normal. The increase in pressure did not appear to be due entirely to the increase in pulmonary vascular resistance but was due equally to the increase of pulmonary flow from approximately twice to three times systemic flow over the interval. Such data are not in agreement with previously conceived ideas. The simplest and most obvious explanation would be an unrecognized right-to-left shunt. It would seem that this is not the only explanation, since the systemic oxygen contents were within normal limits and the cardiac index remained essentially constant over the period of years studied. An explanation which has been suggested is that the size and resistance of the ventricular defect may have increased with growth of the patient and the heart out of proportion to the size and resistance offered by the aortic valvular orifice. These data would seem to indicate that about half the patients in this study exhibit a progressive course.

It may be reasonably hypothesized that a small number of patients have no "latent" period and begin the process from near birth and that others have varying intervals of "latency" from 1 to 15 years. The patients showing no change during the period studied may begin subsequently to take a progressive course. Such data will become increasingly difficult to obtain as more and more children with the defect are subjected to surgery.

Thirty-five patients who survived closure of their ventricular septal defect have been restudied approximately one year following surgery.

Twenty-seven patients on recatheterization showed no residual left-to-right shunt, and in all but three cases there was a significant drop in pulmonary artery pressure consistent with the decrease in pulmonary flow. In three patients there was no drop in pulmonary artery pressure, and calculated total pulmonary resistance increased. From two of these patients there was lung biopsy material, which exhibited intimal proliferation of small pulmonary arterioles.

There were eight patients with demonstrable residual left-to-right shunts, five of whom had significant reduction in pulmonary artery pressure and were noticeably improved. Three of these patients were unimproved.

Growth failure preoperatively was common, and nearly all patients returned to average growth levels postoperatively when the shunt had been closed and pulmonary hypertension was not a prominent feature.

Increased pulmonary vascularity estimated by roentgenogram soon returned to normal when the shunt was closed, but cardiomegaly disappeared less strikingly.

All patients had incomplete or complete right bundle branch block.

**Observations on a Rare Congenital Disorder—Chediak and Higashi's Disease.** GERALD MILLER, M.D.*; STANLEY B. TROUP, M.D.,* and ARTHUR NUNNERY, M.D.,* Rochester, N. Y. Introduced by WILLIAM L. BRADFORD.

Clinical, hematologic, and pathologic observations have been made of a child with a little-known disorder previously described by Chediak as a "new familial and constitutional leukocytic anomaly" and by Higashi as "congenital gigantism of the peroxidase granules." The disease appears to be uniformly fatal in early life.

The manifestations of the disorder in the present case can be conveniently divided into a "latent stage" and a "terminal stage." During the latent stage photophobia, incomplete albinism, and abnormalities of leukocytic granulation were detected. In the terminal stage the clinical picture resembled leukemia, with the development of pancytopenia, hepatosplenomegaly, and neurologic manifestations.

Autopsy in the present case revealed hepatosplenomegaly. Microscopically there was erythrophagocytosis in the spleen, bone marrow, and lymph nodes; hypochromatosis of the choroid of the eye, and widespread infiltration of tissues by leukocytes and monocytes. In the brain these cells were predominantly perivascular. There was a dense infiltrate of similar cells in the meninges, choroid of the eye, and optic nerve.

The familial occurrence of the disease in the previously published cases, which occurred in consanguineous marriages, raises for consideration the possibility that the disorder is genetically determined. Early recognition of the disease is possible and would allow several years in some cases for more extensive clinical and histochemical studies.

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**Can the Origin of Congenital Malformations Be Dated by Their Morphological Characteristics?** Josef Warkany, M.D., Cincinnati.

During prenatal life the embryo or an embryonic part may be more vulnerable at certain phases of development than at others. The existence of such "critical periods" has been demonstrated in many experiments in which embryos were exposed to teratogenic factors for short periods only. The types of malformation produced in this way depend in many cases upon the time of treatment rather than upon the properties of the teratogenic agent employed. A certain time-specificity can be recognized also in malformations produced by German measles, although it cannot be shown for all cases and for all the organs affected. As a result of such experiments and observations numerous statements have been made in recent years in the medical and popular literature which imply that most congenital malformations are due to "stress" at critical periods and that it is possible to determine the date of injury to the fetus by the morphological characteristics of abnormalities or syndromes observed after birth.

Such statements are based on various erroneous assumptions. They neglect to take into consideration that an organ may have several critical periods of development, that chronic injurious factors which stay with the embryo may merely manifest themselves at critical periods, and that many malformations are already determined at the time of conception. For instance, open ductus arteriosus may be caused by German measles in the first trimester of gestation, but it does not become a malformation until birth. In animal experiments it has been shown that external events can cause cleft palate when applied just before the time of palate closure; but it has also been shown that this malformation can be induced at various other periods preceding palate closure. Thus, the time of causal determination of malformations may differ greatly from the time of their anatomical manifestation. This distinction must be emphasized, since it is of practical importance. The concept that human congenital malformations can be dated generally according to an embryological timetable of "critical periods" may lead to accusation of useful medical procedures or harmless accidents in early pregnancy as responsible for congenital defects with which they have no causal relationship.

**"Vital Capacity" and Lung Compliance in Normal Newborn Infants and Infants with "Hyaline Membrane Syndrome."** J. E. Dripps, M.D.,* Boston; R. B. Cherry, M.A.,* Boston; J. F. Lucey, M.D.,* Burlington, Vt.; S. Segal, M.D.,* Vancouver, B. C., Canada; J. M. Sutherland, M.D.,* Cincinnati, and C. A. Smith, M.D., Boston.

A method for the measurement of lung compliance was reported to the Combined Pediatric Meeting held in Quebec, Canada, in 1955. Lung compliance is here defined as the ratio of tidal volume to change in intraesophageal pressure measured between points of no flow. Further experience with this method has shown that the same apparatus may be used to estimate vital capacity in the newborn infant. This is done by stimulating the infant to cry, as during resuscitation procedures, and measuring the recorded volume change between maximum expiration and maximum inspiration. A volume change so obtained is assumed to approach the vital capacity of the infant; however, since it is not obtained by the standard procedure used for older children and adults, the term is placed in quotation marks.

At the present time 35 studies to determine both lung compliance and "vital capacity" have been performed on 25 normal infants, and 15 such studies, on 12 infants with the clinical picture of "hyaline membrane syndrome." The regression equation calculated from data on the normal infants has the formula $C=0.03V_{vc}+0.2$, where C=pulmonary compliance in milliliters per centimeter of $H_2O$ and $V_{vc}$="vital capacity" in milliliters. The correlation between these two variables is 0.82. Therefore, in the normal infant "vital capacity" may be a useful indication of lung compliance. In those infants with respiratory distress thus far studied, both compliance and "vital capacity" were reduced, the decrease in "vital capacity" being relatively less than the decrease in compliance in the majority of such determinations. In serial measurements made during recovery from respiratory distress, clinical improvement (as judged by the appearance of the infant) has been more rapid than improvement in compliance and "vital capacity."

**Pathogenesis of Congenital Polycystic Kidneys.** Edith L. Potter, M.D., Chicago.

Study of 125 cases in which cysts were present in the kidneys of fetuses or young infants fails to confirm, as a cause, either of the two most commonly accepted theories. Cysts are a result of many causes; these can be divided into four main groups. Those which are a result of (1) general or local obstruction to outflow of urine, (2) an abnormal interaction between the metanephric bud arising from the mesonephric duct and the stromogenic and nephronogenic elements of the metanephric blastema, (3) hamartomatous proliferation of renal tubules, and (4) physiologic dilatation of localized segments of nephrons or collecting tubules.

When kidneys in which the cysts are secondary to demonstrable obstruction are eliminated, the

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majority of polycystic kidneys fall into Group 2. In this group the appearance of the kidneys is extremely variable. If the metanephric bud is abnormal the metanephric blastema does not respond normally and the extent of abnormality depends on the degree of abnormality of the metanephric duct. Conversely, either the stromogenic or nephronogenic portions of the metanephric blastema may fail to develop normally, with resultant hypoplasia or hyperplasia of either element even though the metanephric duct is intrinsically normal.

Hamartomatous proliferation of tubules is often described as the typical polycystic kidney of the newborn but in this series was encountered only five times.

There is no evidence that warrants differentiating multicystic from polycystic kidneys.

**Six-Year Follow-Up of One Type of Prolonged Intermittent Steroid Therapy in "Nephrosis."** KURT LANGE, M.D.*; LAWRENCE B. SLOBODY, M.D., and EUGENE J. WENK, M.A.,* New York.

Forty-six of our cases, 36 children and 10 adults, with the nephrotic syndrome ("pure" nephrosis and the nephrotic stage of glomerulonephritis) were treated with the following regimen. There was an initial course of corticotropin (ACTH), 100-200 units per day, given for 10 to 21 days, and, after complete diuresis had occurred, maintenance therapy consisting of 300 to 400 mg. of cortisone per day for three successive days out of each week. This maintenance therapy was carried out for 12 to 18 months. The average time of observation after onset of maintenance therapy was 31.8 months.

The mortality expected in this group on maintenance therapy on the basis of the mortality occurring in a similar group not treated with steroids or treated with steroids only when edema was present, would have been 12.8 deaths during the period of observation. There has been one death in our group on maintenance therapy. Tested by the $\chi^2$ method, the possibility of this distribution occurring by chance was found to be less than 1:1000 ($\chi^2=10.87$; $P<0.001$).

Function tests such as urea clearance done at the end of maintenance therapy and at intervals subsequently do not indicate a progressive loss of renal function during this period of observation. Early treatment with corticotropin to induce complete diuresis followed by maintenance therapy with steroids seems indicated. In three cases resistant to repeated courses of intramuscular corticotropin complete diuresis was achieved by the intravenous infusion of 30 to 40 units of corticotropin over an 8-hour period each day for 10 to 12 days.

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**A Syndrome of Congenital Deafness with Characteristic Associated Defects (Waardenburg's Syndrome).** ANGELO M. DIGEORGE, M.D.*; RICHARD W. OLMSTED, M.D.*; VICTOR C. VAUGHAN III, M.D.*; ROBISON HARLEY, M.D.,* and MILTON BRUTON, Ph.D.,* Philadelphia. Introduced by JAMES B. AREY.

In 1951 Waardenburg described a syndrome consisting of deafness, heterochromia iridis, white forelock, lateral displacement of the lacrimal puncta, a broad nasal root, and medial hyperplasia of the eyebrows. The syndrome appears to be inherited as an autosomal dominant of variable expressivity.

This syndrome has not been reported previously in Negroes. A detailed report of its occurrence in two Negro families will be made. Five additional typical instances of this syndrome will be shown which were discovered as a result of a survey of an institution for deaf children in the Philadelphia area. It is probable that about 1.5% of institutionalized deaf children have this genetic abnormality. Results of detailed audiometric and ophthalmologic examinations on all of the affected children will be presented.

Evidence will be presented that this syndrome results from a genetically determined defect in pigment metabolism and that the nerve deafness is related to this pigmentary defect.

**Blood Gas Studies in Patients with Fibrocystic Disease of the Pancreas: Indications and Contraindications for Oxygen Therapy.** ERIKA BRUCK, M.D.,* Buffalo. Introduced by MITCHELL I. RUBIN.

Partial pressures of $CO_2$ and oxygen in arterial blood are controlled by respiration and in turn constitute the stimuli for the nervous regulation of respiratory movements. In diseases affecting respiratory function, such as fibrocystic disease of the pancreas, $CO_2$ and $O_2$ tensions may be deranged to a different degree, depending on the mechanism of the respiratory dysfunction.

The type of dysfunction may be recognized by analyzing the gas tensions in arterial blood and alveoli.

In seven patients with fibrocystic disease of the pancreas, pH, $CO_2$ content, $pCO_2$ and $pO_2$ were determined in arterial blood, and alveolar $pO_2$ and alveolar-arterial $pO_2$ differences were calculated. In all cases, even the mildest ones, the alveolar-arterial $O_2$ difference was increased to two to five times the normal value, and arterial $pO_2$ was below normal. pH and $CO_2$ tensions were normal in five of these patients and indicated minimal $CO_2$ retention in the other two.

This finding is not compatible with the assumption that reduced alveolar ventilation due to generalized obstruction of airways is the chief res-

piratory disturbance in these patients. With pure, generalized hypoventilation, $CO_2$ tension should be more elevated than $O_2$ tension is reduced and the alveolar-arterial $O_2$ difference should be normal. Either a diffusion barrier between alveoli and blood —such as pneumonic exudate—or a mixture of blood from unventilated portions of the lung with blood from ventilated parts will result in a large alveolar-arterial $O_2$ difference without affecting $pCO_2$ much. With inhalation of high concentrations of $O_2$, the alveolar-arterial $O_2$ difference will increase further in cases of uneven ventilation-perfusion ratio but will remain unchanged in cases of a diffusion barrier.

Five other patients with fibrocystic disease of the pancreas were studied at two different levels of oxygen in the inspired air. These patients were sicker than the first group; they all had received oxygen therapeutically. They all had $CO_2$ retention, indicating reduction of total alveolar ventilation. In only one of these patients could the alveolar $pO_2$ be determined on two occasions at both levels of $O_2$ inhalation; the alveolar-arterial $O_2$ difference both times increased considerably with inhalation of 36% to 38% $O_2$. In all five patients the arterial $pO_2$ was raised only a little by the $O_2$ therapy, although this small amount sometimes made the difference between a level compatible with life and one that was not. In all patients with $CO_2$ retention, inhalation of high concentrations of $O_2$ produced depression of respirations and further aggravation of the respiratory acidosis. In one case the parents administered 100% $O_2$ from a mask to a child with severe respiratory acidosis; unconsciousness and apnea occurred within five minutes and were reversed by artificial respiration.

It is concluded that the primary respiratory disturbance in fibrocystic disease is uneven distribution of ventilation in relation to perfusion. In advanced cases, when obstruction becomes generalized, hypoventilation ensues and causes respiratory acidosis. In cases of respiratory acidosis, raising the arterial $pO_2$ with $O_2$ therapy results in further depression of respirations. 100% $O_2$ may raise the arterial $pO_2$ sufficiently to cause apnea.

**Composition of Mucoproteins from Duodenal Fluid of Children With and Without Cystic Fibrosis of the Pancreas (CFP).** ZACHARIAS DISCHE,* PAUL DI SANT'AGNESE, M.D., and JOSHUA YOULUS,* New York.

It has been previously shown that duodenal fluid of children with CFP yields, after precipitation with ethanol benzene, a water-insoluble mucoprotein fraction. Further investigations showed that the water soluble mucoprotein fraction of duodenal fluid is partly precipitated by trichloracetic acid (TCA). The TCA-insoluble fraction of children with CFP differs in composition from that of controls, as the ratio of protein to carbohydrate is three times as high in the latter as in the former. This suggests the possible presence in the fluid of controls (but not in patients with CFP) of a protective protein which prevents in controls the denaturation of one part of mucoproteins which takes place during ethanol benzene precipitation in fluids of CFP patients. Fractionation of the water and TCA-soluble mucoprotein fraction of CFP patients and controls by ethanol and acetone yielded four subfractions which differed significantly in their solubility. All fractions contained methyl pentose, hexosamine, hexose and sialic acid, and protein. In the fraction soluble in 90% ethanol, however, all the protein could be separated from the carbohydrate by acetone. The ratio of carbohydrate to protein in other fractions varied between 1.5 and 2. The methyl pentose was identified by paper chromatography with two solvents as fucose; the hexose constituents by paper chromatography and fermentation tests, as galactose, mannose, and small amounts of a third hexose, probably glucose. The quantitative analysis of all fractions by specific color reactions showed that the sugars were present in the form of at least two mucopolysaccharides, one of which contained predominantly galactose and only small amounts of other hexoses and was present in fractions insoluble in 50% and 67% ethanol, respectively. The other contained predominantly mannose and was present in the fraction soluble in 90% ethanol. The molar ratio of fucose to hexosamine was about 1:2 in all fractions, whereas the amount of hexose and sialic acid in controls increased throughout with solubility in ethanol. This heterogeneity in the composition of the mucopolysaccharide fractions, as far as hexose and sialic acid are concerned, may be due to an enzymatic breakdown of a highly asymmetric high polymer which contains a backbone of fucose and hexosamine in a molar ratio of 1:2. The mucoprotein fractions from the fluid of CFP patients differed from those of controls by a significantly higher ratio of sialic acid to hexosamine and by a different distribution of this acid among the individual fractions. This suggests a possible role of sialic acid in the determination of solubility as well as sensitivity to denaturing agents of mucoproteins of mucus.

**The Arterial and Venous Glucose-Tolerance Test in Obese and Nonobese Children.** HEYWORTH N. SANFORD, M.D.; ABOL G. MOSTOFI, M.D.*; I. PAT BRONSTEIN, M.D.,* and GERTRUDE ASROW, B.S.,* Chicago.

It is generally believed that the glucose tolerance of children over 5 years of age is similar to that of adults. Possibly because of this assumption, the study of glucose tolerance for this age group is meager. A search of the literature failed to reveal

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any study of a glucose-tolerance test for this age group (5 to 14 years). The criteria by which the glucose-tolerance test is interpreted, in textbooks of pediatrics, are based upon the work of McLean and Sullivan and of Livingston and Bridge on infants and children under 3 years of age.

The arteriovenous glucose tolerance was studied simultaneously in 8 obese and 10 nonobese children between the ages of 4 and 14 years. The following observations were made: 1. The peak of the glycemia was slightly higher in the means of the nonobese group. 2. The blood levels of the glucose returned to fasting levels in three hours in 80% of the nonobese group. 3. In the obese group only 25% of the blood levels of the glucose returned to fasting levels in three hours. 4. The difference between the glucose levels of the venous blood at fasting and at three hours was more conspicious and statistically significant.

The response of the children of this age group to the glucose meal is different from that of adults. Their fasting blood sugar is lower, and the rise of blood sugar is faster. The peak is reached in half an hour and is higher than in adults. The criterion for the normal arterial glucose-tolerance test is a fasting blood glucose level of 87 mg/100 cc., that should not exceed 100 mg/100 cc. or be lower than 80 mg/100 cc. The increase of blood sugar after a glucose meal should be from 40% to 140% of the fasting level. The blood glucose should return to a fasting level in three hours if the recommended dosage is used.

**Pulmonary Resections in Cystic Fibrosis of the Pancreas: Prelobectomy and Postlobectomy Studies in Six Patients.** H. Shwachman, M.D.*; L. L. Kulczycki, M.D.,* and J. M. Craig, M.D.,* Boston. Introduced by Sidney Farber.

Six patients with cystic fibrosis of the pancreas, ranging in age from 2 years to 13 years, are presented. The two youngest patients are of particular interest because these conditions were diagnosed in early infancy and therapy was directed for this condition. Lobar atelectasis involving the right middle lobe was detected in each case and persisted in spite of numerous attempts to correct this condition. Surgery was accordingly performed when these infants were 16 months and 22 months of age. Their present condition is satisfactory. The appearance of lobar atelectasis in small babies with cystic fibrosis affects the prognosis unfavorably. We felt that surgical removal was justified under these circumstances.

The four other patients had bronchiectatic changes involving either the left or the right lower lobe. In two patients the diagnosis of cystic fibrosis was made 14 and 18 months after operation; respectively. In view of the relative infrequency with which only one segment of the lung is severely affected in this generalized disease, the indication for the removal of the bronchiectatic area is not a common problem.

We should like to point out that at the present time simple diagnostic procedures for cystic fibrosis are available, such as the finger imprint method or the sweat test, so that any child subjected to lobectomy for bronchiectasis of unknown cause should have the benefit of these diagnostic procedures prior to operation.

**The Treatment of the Nephrotic Syndrome with Triamcinolone.** Leon Hellman,* Barnett Zumoff, M.D.*; Norman Kretchmer, M.D.*; Arnold Minsky, M.D.,* and Benjamin Kramer, M.D., New York.

A new synthetic steroid, 16-α-hydroxy,9-α-fluoro,δ-1-hydrocortisone (Triamcinolone, Lederle), exhibits antirheumatic action equal or superior to other currently available compounds. In therapeutic doses, it is devoid of sodium-retaining or potassium-losing properties, while producing only minimal changes in nitrogen and calcium balance. Because of these clinically desirable properties, Triamcinolone has been used in the treatment of five children with the nephrotic syndrome. The subjects ranged in age from 1½ to 4 years and had typical findings of nephrosis, including edema, hypoalbuminemia, hyperlipemia, hypercholesteremia, proteinuria, and ESR elevation. One had elevated blood urea nitrogen. Following suitable baseline studies, 4 to 20 mg. of Triamcinolone was given each day orally in four divided doses. Four subjects had a complete diuresis which began on the 11th or 12th day of therapy. The single patient with the elevated BUN level did not respond. Beginning at the time of diuresis, the chemical abnormalities began to regress and in three weeks serum albumin, cholesterol, total lipids, ESR, and urine protein excretion were within normal limits. In these four subjects, there was no fluid retention, electrolyte disturbance, blood pressure elevation, or other undesirable effects. The steroid was discontinued after all the laboratory findings had become normal. There have been no clinical or chemical recurrences in these four patients with follow-ups ranging from two to eight months. The prompt and prolonged remissions, together with the absence of undesirable side-effects, indicates that this successful use of Triamcinolone in the treatment of the nephrotic syndrome merits further study.

**Antihemophiliac-Factor Deficiency in a Female: Report of a Case.** Joseph J. McGovern, M.D.,* Boston, and Arthur G. Steinberg, Ph.D.,* Cleveland. Introduced by John D. Crawford.

The present report concerns the identification of antihemophiliac-factor deficiency in a girl suffering

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from a hemorrhagic disorder clinically resembling classical hemophilia. Following a tonsillectomy there was profuse hemorrhage which required 3 pt. of blood for its control. The only demonstrable abnormalities in coagulation were an abnormal thromboplastin generation test and a reduced amount of AHF(5%) in the plasma. Electrophoretic studies of the patient's plasma did not disclose the $\alpha$-x anomaly, and cytologic studies of her buccal mucosa and polymorphonuclear leucocytes confirmed the conclusion reached on morphologic grounds that the patient is female.

Hematologic and genetic investigation of the family revealed the maternal grandfather to have mild classical hemophilia, and blood grouping studies eliminated the possibility that he was the biologic father. The patient is probably heterozygous for an allele of classical Hemophilia and exhibits an extreme AHF deficiency. This genetic hypothesis cannot be tested, however, until the patient has offspring and then only if she has a normal son.

The data support the suggestion that the mutant gene carried by the patient is incompletely recessive and that she has a degree of clinical expression of hemophilia not observed or previously reported in female carriers. It would be advisable to restrict the term "hemophilia in the female" to those persons who can be shown to be homozygous for the sex-linked gene leading to classical hemophilia in the male. The others, such as this patient, might best be referred to as suffering AHF deficiency.

**Circulation Time in Infants and Children with the Dermofluorograph.** JAMES TANG, M.D.,* and LAWRENCE B. SLOBODY, M.D., New York.

Fluorescein has been widely used for determining circulation time in newborns, infants, and children. However, it has depended on a subjective evaluation of the end-point, with consequent disagreement among different observers. There has also been the inconvenience of having to use a darkened room.

Lange and Mohl have developed a dermofluorograph which provides an objective measurement of circulation time using fluorescein. The dermofluorograph consists of a photocell aligned to a long-wave ultraviolet light source; the output of the photocell is electronically amplified and recorded on a strip chart recording galvanometer. The time elapsing from the intravenous injection of a fluorescein solution to its arrival in the face or extremity (arm-to-face or arm-to-leg circulation time) can thus be determined objectively. The instrument is portable, and the test can be performed at the bedside, without the necessity for special rooms or precautions. The tests may be repeated at three-minute intervals; the results are reproducible with a maximal deviation of $\pm 5\%$.

In our previous studies using fluorescein, but with subjective evaluation of the end-point, we found arm-to-lip time in the 8- to 13-year-old group of 8.3 to 16 seconds; from 3 to 7 years, 7 to 15 seconds; in newborn infants, umbilical vein to lip, 3.1 to 7 seconds.

Other observers have reported similar results, with the possible exception of Lesser and associates, who found, in 1- to 5-day-old infants, the arm-to-conjunctiva time to be 6 to 14.4 seconds.

We have studied circulation time in these age groups using fluorescein with the dermofluorograph. In normal children from 8 to 12 years of age the range for arm-to-face time was 9.5 to 16.7 seconds. Since arm-to-face time is not applicable in Negro children, arm-to-sole times have been studied to establish values for this circuit. In patients aged from 8 to 12 years, arm-to-sole times ranged from 16.2 to 31.8 seconds.

**Physiologic Hyperbilirubinemia in Negro and White Premature Infants.** GERALD H. HOLMAN, M.D.,* Baltimore. Introduced by LAWSON WILKINS.

The appearance of clinical icterus and chemical hyperbilirubinemia in the newborn infant is recognized as being an extremely common occurrence. Most of the recent work has revealed a higher incidence in the premature than in the full-term infant, although some conflicting evidence does exist. Also, the occurrence of kernicterus in many prematures has been causually related to this period "physiologic hyperbilirubinemia."

Since the majority of clinical and investigative work suggests that this hyperbilirubinemia is related to the relative inability of the newborn infant's liver to excrete bilirubin, it has been stated that the degree of bilirubinemia reached is related to the functional maturity of the individual child. If this is true, then the higher levels generally reached in the premature infant can be more easily understood.

The present study was undertaken to investigate the following: the occurrence of kernicterus in the premature nursery of the Johns Hopkins Hospital, the role played by maturity (based on weight) in determining the degree of hyperbilirubinemia reached, and the relation of racial stock (Negro or white) to the degree of hyperbilirubinemia.

Twenty-five Negro and fourteen white premature infants were studied. Blood group incompatibilities, including Rh and ABO, were excluded as causes of the hyperbilirubinemia. Syphilis and sepsis were also excluded. Plasma micro total and direct-reacting bilirubin levels and hematocrit or hemoglobin levels were estimated every 24 to 30 hours in each infant until the peak of bilirubinemia had

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passed. Bilirubin estimations were then made every 48 to 60 hours until the total bilirubin was below 2 mg. per 100 cc.

There were no cases of clinical kernicterus despite the fact that 23 infants (59%) had total plasma bilirubin levels that reached 18 mg. per 100 cc. or higher. Follow-up studies at one year of age on these infants so far has not revealed children with neurological deficits attributable to neonatal hyperbilirubinemia per se.

Comparison of the mean bilirubin levels reached by the most immature group (under 1500 gm.) with those reached by the most mature group (2000 to 2500 gm. for white and 2000 to 2350 gm. for Negro infants) revealed significantly higher levels in the least mature group for both racial stocks.

Comparison of the most immature white infants with the most immature Negro infants revealed a significantly higher level of the mean bilirubin in the white group. A similar but less striking finding appeared on comparison of the most mature white and Negro groups. There was no significant difference between the moderately mature (1500 to 2000 gm.) Negro and white infants.

The significance of these findings in relation to the functional maturity of the infants will be discussed. Some possible basic etiological factors for the "hepaticimaturity" will be presented and future avenues for investigation will be outlined.

**Esophageal Motility as Studied Cinefluorographically in Patients with Esophageal Atresia and Tracheoesophageal Fistulas.** JOHN A. KIRKPATRICK JR., M.D.,* Philadelphia. Introduced by JAMES B. AREY.

Pulmonary infection is a common and expected complication of tracheoesophageal fistula and/or esophageal atresia or stenosis in the newborn period. Preoperative cinefluorographic studies of the contrast-filled esophagus in a patient with tracheoesophageal fistula without esophageal atresia will be presented in addition to postoperative studies in other patients.

The findings suggest that inherent defects in the motility of the esophagus may be associated with the presence of such anomalies. The significance of this finding as related to preoperative and postoperative complications will be discussed.

Moving pictures utilizing cinefluorographic techniques will be used to illustrate the defect under discussion.

**A Reevaluation of the Indications for Replacement Transfusion in the Prevention of Bilirubin Encephalopathy.** WILLIAM J. WATERS, M.D.,* Syracuse, N. Y. Introduced by JULIUS B. RICHMOND.

This study was undertaken to reassess the proper role of replacement transfusion in the treatment of hemolytic disease of the newborn due to Rh incompatibility. On the basis of the conviction that bilirubin is toxic to the newborn brain, I decided to use the infant's ability to handle bilirubin as the main criterion for transfusion. A demonstrated rise of serum bilirubin toward critical levels early indicated the need for replacement transfusion (20 mg. per 100 cc. was regarded as a critical level). As a result, conservative management without transfusion was effective in a number of cases which by the usual criteria would have had a replacement transfusion.

The cases studied cover a three-year period (1953-1956) in a 250-bed general hospital. There were 56 cases with a positive Coombs' test subject to analysis. This group is subdivided into 31 cases supervised by me and 25 cases supervised by other staff members, who tended to use the more liberal accepted criteria. In the former group, 11 (35.5%) were managed conservatively without transfusion and no untoward sequelae developed. In the latter group, only four (16%) were managed conservatively, again with good results. In the replacement-transfusion groups there were two cases of brain damage, one in each series.

The one patient in my group died at 76 hours of age, with staining of the brain, despite four replacement transfusions. The hemogram at birth revealed 6.7 gm/100 cc. of hemoglobin. If the arbitrary value of 17.6 gm/100 cc. is used as a normal value, the minimum destroyed hemoglobin would be 10.9 gm/100 cc. Accepting 300 cc. as the total blood volume, the minimum amount of destroyed hemoglobin would be 32.7 gm. The latter obviously had taken place in utero and therefore served as the source for bilirubin even though the initial replacement transfusion was done at 2 hours of age. Potentially more than 1 gm. of bilirubin was presented to the infant for clearance. The replacement transfusions accomplished the removal of only a fraction of this amount, and thus the serum level rose above 20 mg. per 100 cc. each time, with the infant remaining severely jaundiced. The level before death was 23 mg. per 100 cc. Postmortem examination revealed yellow staining of the brain. This case suggests that on occasion an overwhelming load of bilirubin may be presented to the newborn with disease and that replacement transfusion is inadequate in such an instance in preventing bilirubin encephalopathy.

The maternal anti-Rh titers were recorded and showed wide variation, with high titers occurring in instances where conservative management was equally effective as replacement transfusion.

* By invitation.

The analysis of the results of this study leads to the following conclusions: 1. Maternal titer values and/or a positive Coombs' by themselves are not an indication for replacement transfusion. The main emphasis should be placed on the clinical condition and course of the newborn infant, particularly his ability to handle bilirubin. 2. These cases need close supervision from the clinical and laboratory standpoint and should be referred to a center if the facilities are not available for such supervision. 3. A demonstrated rise of serum bilirubin toward critical levels early, particularly within 12 hours, remains the best criterion for need of blood replacement in questionable cases. 4. Rarely, replacement transfusions may be inadequate to control the serum bilirubin level and prevent brain damage.

It should be reemphasized that the development of bilirubin encephalopathy is usually between the third and fifth days of life and that the earliest recorded occurrence in the literature is 18 hours of age, the next earliest being 30 hours of age. Therefore, there is no urgency for replacement transfusion in the newborn who is clinically well; a period of careful observation is in order in this instance before a replacement transfusion is undertaken. The procedure itself is not without hazard, particularly in the hands of an unskilled operator.

**Studies in Sickle-Cell Anemia: Hepatic Involvement in Children.** ROLAND B. SCOTT, M.D., and ANGELLA D. FERGUSON, M.D.,* Washington, D. C.

Sickle-cell anemia is a systemic disease in which the basic pathophysiology is thought to be due to the presence of an abnormal hemoglobin which, in the presence of decreased oxygen tension, crystallizes, producing sickling of the erythrocytes with increased viscosity and resultant stasis of the blood. Following slowing of the flow of blood, there is thrombosis, resulting in ischemia, infraction, and hemorrhage of the organ involved, with necrosis of tissue.

Clinically, the liver is palpable in most patients with sickle-cell anemia under the age of 10 years, but during the second decade the liver is usually not enlarged. After the age of 5 years, jaundice is present to a variable degree in more than 50% of the cases and tends to increase with advancing age. The jaundice seems to be due to a hyperbilirubinemia, which may become severer during periods of hemolytic crises. This increase in excretion of bilirubin predisposes to cholelithiasis, which can cause obstruction to the common duct and further hepatic damage.

In a previous publication we called attention to the fact that the plasma volume in sickle-cell anemia is increased, to compensate for a lowered cellular volume, and that the total circulating plasma protein mass in these patients was considerably higher than in normal persons. The elaboration of this large amount of plasma protein in patients with sickle-cell anemia conceivably places an extra load on liver metabolism. The deposition of iron pigment derived from large amounts of transfused blood may cause hepatic dysfunction and even cirrhosis in long-standing cases.

According to Diggs, pathological studies based on autopsy material have revealed that the liver in sickle-cell anemia is usually enlarged, firm, and dark, with a smooth capsule. Microscopically, the capillaries are distended with masses of sickled cells. The Kupffer cells are enlarged and contain sickled cells and pigment. The parenchymal cells show degenerative changes. The interlobular reticulum is increased, and periportal fibrosis and lymphocytic infiltration are commonly noted.

There is, therefore, evidence of liver change in varying degrees in all cases of sickle-cell anemia. Because of the multiplicity of the different functions of liver metabolism and the large size and functional reserve of this organ, one may anticipate difficulty in ascertaining the quantitative interference with liver function during childhood. Nevertheless, we have employed certain selected tests from the usual battery of liver-function tests in an effort to appraise the clinical status of this organ in children with sickle-cell anemia.

The 12 children reported in this paper ranged in age from 2 to 13 years and represented 36 admissions to the hospital during this study. Of the total number of admissions, a palpable liver was found clinically in 13 and clinical icterus of variable degree, in 8, or 22%.

Preliminary examination of the data collected in these cases disclosed only minimal evidence of liver damage; however, this may be significant in view of the youth of the patients.

**Influence of Transfusions on the Presence of Erythropoietic Stimulating Factor (ESF) in the Plasma of Anemic Patients.** PAUL T. MEDICI, Ph.D.*; ALBERT S. GORDON, Ph.D.*; SAM J. PILIERO, Ph.D.*; A. LEONARD LUHBY, M.D.,* and PERIHAN YUCEOGLU,* New York. Introduced by LAWRENCE B. SLOBODY.

These studies were designed to determine the effect of transfusion on the erythropoietic stimulating properties of the plasma from patients with Cooley's anemia. Evidence for the presence of a humoral stimulant of erythropoiesis in the blood and urine of such subjects has previously been reported by our group. These latter observations constitute evidence for the existence of a circulating ESF in man comparable to that observed in laboratory animals rendered anemic. Others have presented clinical and laboratory findings suggesting that such a plasma "erythropoietin" may also

* By invitation.

mediate in humans the secondary polycythemia associated with the chronic hypoxia resulting from certain pulmonary and cardiovascular abnormalities.

Our clinical material consisted of plasma from patients with Cooley's anemia when they were severely anemic and following transfusions with whole blood which brought hemoglobin levels to 10.4 to 12 gm. per 100 cc. The plasmas of normal children of a corresponding age were used as controls.

The assay method for erythropoietic activity employed the measurement of changes in the peripheral red cell count, hemoglobin, hematocrit level, reticulocyte count, and bone marrow nucleated red cell percentages in normal adult rats resulting from the parenteral administration of a protein-poor filtrate of the test plasma. The filtrate was prepared by adjusting the plasma to pH 5.5, boiling for 10 minutes, and discarding the solids. The supernatant was brought to a pH of 7.2. Three to five rats of a modified Long-Evans strain were injected subcutaneously daily with 1.8 to 3.0 ml., equivalent to 3.0 ml. of the original plasma, for 5 to 10 days. Peripheral blood studies on the animals were done prior to, during, and at the end of the study period. Bone marrow examinations were made after killing on completion of the test period.

The results showed marked evidence for erythropoietic stimulation in both the peripheral blood and the bone marrow of the test animals injected with filtrates prepared from plasma of severely anemic subjects with Cooley's anemia. Filtrates from normal plasma were uniformly inactive. Following transfusion to levels indicated above, the erythropoietic stimulating properties of the plasma from patients with Cooley's patients were no longer evident.

**The Effect of Humidity on Survival of Newly Born Premature Infants.** WILLIAM A. SILVERMAN, M.D.,* and WILLIAM A. BLANC, M.D.,* New York. Introduced by CONRAD M. RILEY.

A controlled clinical trial was designed to compare the effects of two contrasting conditions of humidity upon respiratory performance, survival, and morbid anatomy among newly born premature infants. The first of these trial conditions of humidity approximated the one which had been generally used in premature nurseries for about 20 years. The contrasting condition had been advocated less than three years previously as a method of preventing or reducing the severity of respiratory distress among such newborns. The study was conducted in the premature nursery of the Babies Hospital from December, 1954, to March, 1956. Three hundred twenty-four infants admitted to the nursery during this period constituted the population of the study. Allotment into the treatment categories was made by systematic randomization. The contrasting conditions of humidity were 30% to 60% R. H. (relative humidity) vs. 80% to 90% R. H. Environmental temperature (28.3 to 29.4 C) was the same in both categories. The conditions of the trial were maintained from the time of admission to the nursery until the age of 120 hours.

One hundred sixty infants were assigned to 30% to 60% R. H., and 164, to 80% to 90% R. H. The two groups were comparable with respect to sex, race, birthplace, economic level, birth weight, mother's age, birth rank, stated cause of prematurity, route of delivery, position at the time of delivery, age on admission to the nursery, incidence and degree of dyspnea on admission to the nursery, and body temperature on admission to the nursery.

The incidence and degree of retractions from admission to 72 hours of age were essentially the same in the two groups. There were small but consistent and significant differences in respiratory rates at equivalent ages in the two groups. The 80% to 90% R. H. infants had rapider rates of respiration. There was no significant difference in the initial weight loss in the two humidity categories. Although the environmental temperatures were the same in both trial classes, the body temperature of infants in 80% to 90% R. H. was slightly but significantly higher than the temperature of infants in 30% to 60% R. H.

There was a significant difference between the mortality rates of the two classes during the trial period. Infants who were placed in the 80% to 90% R. H. condition died at a significantly lower rate than was observed for the 30% to 60% R. H. group.

No significant differences were noted in the incidence of positive postmortem cultures nor in the distributions of microorganisms obtained on culture, of infants who died during the trial in the two humidity groups. The pathologic diagnoses at necropsy among the infants who died during the trial period did not differ essentially in the two opposing groups.

On the basis of the above observations we have formulated the hypothesis that the major effect of 80% to 90% R. H. on premature infants in the first five days of life is that of reducing heat loss and that it is this effect which is responsible for the lower mortality observed in this environmental condition. Tests as to the validity of this hypothesis are in progress.

**Bilirubin Toxicity: Potentiation by Sulfadiazine and Sulfisoxazole; Inhibition of Ameboid Motion of Leukocytes; Interference with Clotting of Blood; Local Necrosis.** LOIS JOHNSON, M.D.,* and RICHARD DAY, M.D., Brooklyn.

In 1956 Silverman and co-workers reported an epidemic of kernicterus in premature infants which

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TABLE 1.—*Effect of Bilirubin, Sulfadiazine, and Sulfisoxazole in Newborn Albino Rats*

| | Injected, No. | Living, No. | Dying | |
|---|---|---|---|---|
| | | | No. | % |
| Group 1, bilirubin + sulfadiazine | 23 | 4 | 19 | 83 |
| Group 2, bilirubin + sulfisoxazole diethanolamine | 26 | 2 | 24 | 92 |
| Group 3, bilirubin + sodium sulfisoxazole | 23 | 3 | 20 | 87 |
| Group 4, bilirubin + saline | 70 | 54 | 16 | 23 |
| Group 5, bilirubin vehicle + sulfadiazine | 9 | 9 | 0 | 0 |
| Group 6, bilirubin vehicle + sulfisoxazole diethanolamine | 7 | 7 | 0 | 0 |

seemed to have been provoked by administration of sulfisoxazole (Gantrisin). Prompted by this, we gave six groups of newborn albino rats twice-daily injections as follows: Group 1, bilirubin, 0.05 to 0.15 mg. per gram, plus sulfadiazine, 200 mg. per kilogram; Group 2, same bilirubin injections plus sulfisoxazole diethanolamine, 400 mg. per kilogram; Group 3, same bilirubin injections plus sodium sulfisoxazole, 500 mg. per kilogram; Group 5, same bilirubin injections plus saline as dummy injection; Group 6, sulfisoxazole diethanolamine, 400 mg. per kilogram plus dummy bilirubin vehicle. The results are given in Table 1.

Ameboid activity of human leukocytes was tested by the method of Lapin and Horonick. The results are given in Table 2.

TABLE 2.—*Ameboid Activity of Human Leukocytes*

| Additions to Plasma | Granulocytes | | | | | Clumps of Nonmotile Cells & Platelets | Distortion of WBC |
|---|---|---|---|---|---|---|---|
| | Counted, No. | Actively Motile, No. | Sluggish, No. | Nonmotile, No. | Sluggish or Nonmotile, % | | |
| Bilirubin vehicle | 162 | 154 | 9 | 3 | 7 | None | None |
| Bilirubin, mg./100 cc. | | | | | | | |
| 10-25 | 85 | 73 | .. | 12 | 14 | None | None |
| 25-35 | 101 | 41 | 54 | 6 | 60 | Occasional | None |
| 35-55 | 85 | 21 | 39 | 25 | 73 plus clumps | Many | Present |

Blood clotting ceases entirely at bilirubin concentrations above 100 mg. per 100 cc. There is little or no effect below 80 mg. per 100 cc.

Subcutaneous or intraperitoneal bilirubin in concentrations of 60 to 400 mg. per 100 cc. causes local tissue injury; when the rat dies, blood concentrations are below neurotoxic levels and kernicterus does not appear. Death may result from some other mechanism, perhaps shock.

**Pathogenesis of Nephrotic Hyperlipemia.** WALTER HEYMANN, M.D.; L. W. MATTHEWS, M.D.*; A. B. BERGMAN,* and GERALD NASH,* Cleveland.

It has been recently proposed that in the nephrotic syndrome there is a causal relationship between the decreased plasma albumin concentration and the hyperlipemia. It has furthermore been suggested that, in the experimental disease of the rat, the nephrotic hyperlipemia may be explained by an inability of the liver to take up plasma lipids normally (Byers, Friedman, and Rosenman). These two hypotheses stimulated studies that yielded the following results in rats in whom nephrotic renal disease had been induced by antikidney sera obtained from rabbits:

1. No correlation between severity of hypoalbuminemia and hyperlipemia was noted in 20 nephrotic rats with well-established renal disease.

2. Total lipid, cholesterol, serum protein, and serum albumin values were obtained in 26 rats, 2, 4, 6, 8, and 24 hours after the injection of nephrotoxic sera. Hypoalbuminemia did not precede the development of the hyperlipemia.

3. For a period of 10 days, eight nephrotic rats were given 4 cc. of protein containing nephrotic rat urine twice daily by intraperitoneal injection. The plasma lipid concentration decreased in all animals markedly. When eight nephrotic rats were injected with protein-free urines obtained from control animals, plasma lipid concentration decreased in five rats to the same extent. In another group, eight nephrotic rats were treated with saline injections. Plasma lipid concentration decreased in two. Bleeding of eight nephrotic animals without further treatment did not alter blood lipid concentration appreciably. In a last group, eight nephrotic animals received 4 cc. of a 6% dextran solution twice daily by intraperitoneal injection for 10 days. Plasma

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lipid concentration decreased markedly in all rats so treated.

We believe that hypoalbuminemia and hyperlipemia as manifestations of the nephrotic syndrome develop concomitantly. A causal relationship between these two manifestations has not been established by our studies.

Nineteen nephrotic rats were given a $C^{14}$-labeled trilaurin emulsion by intravenous injection. The clearance of this fatty acid from the blood stream and the uptake in liver, kidney, and remaining fat depots were determined after 1, 2, 4, 12, and 24 hours. In nephrotic rats the clearance from the blood and the uptake by the liver progressed at normal rates. An inability of the liver to take up this fatty acid was not noted in nephrotic rats.

**Metabolic Studies in Fat Deficiency.** THEODORE C. PANOS, M.D.; JOHN C. FINERTY, Ph.D.*; GARNER F. KLEIN, M.A.,* and RICHARD L. WALL, B.A.,* Galveston, Texas.

In order to expand and correlate previous experimental work relating to increased metabolism characteristic of fat deficiency, male weanling rats, in groups of 25, were placed on the following diets: I, fat-free, ad libitum; II, "fat-free plus fat, isocaloric"—diet as in Group I with cottonseed oil substituted isocalorically for sucrose to provide 30% of calories as fat; total intake isocaloric with that of Group I; III, "fat-free plus fat, equal weight"—diet as in Group II, but fed in restricted amount to maintain body weight equal to average weight of Group I; IV, "fat-free plus fat, ad libitum"—diet as in Group II, but fed ad libitum; V, Laboratory Chow (Purina) ad libitum, for over-all comparison with known "adequate" diet.

Caloric and water intake were recorded daily. Basal oxygen consumption was determined weekly in eight animals from each group. After 23 weeks, all endocrine organs and accessories, liver, heart, kidneys, serum, and skin were taken for special studies.

The fat-free (Group I) animals achieved maximum weight which was 67% of that of Groups IV and V, whereas the isocalorically fed group (Group II) achieved 90%. Although Groups I and II were fed isocalorically, total weight gain of the latter was 33% greater. Group III maintained average weight equal to that of Group I on 10% less calories. Fat-deficient animals consumed approximately 20% more calories per square meter per 24 hours than those in Group IV or Group V. Basal oxygen consumption of the fat-free rats averaged 33% to 50% greater than all other groups. This evidence of caloric inefficiency finds further expression in the ratio of caloric intake per gram of body weight gain, which in control animals is 60% that of fat-deficient animals. Water consumption in the fat-free animals averaged approximately 1000 ml. per square meter per 24 hours, compared with approximately 500 ml. per square meter per 24 hours in control groups.

The following additional experiment was undertaken in an attempt to evaluate relative importance of increased insensible water loss (IWL) in the total picture of energy loss and to check Sinclair's theory of bidirectional increased skin permeability to water in fat-deficiency. Three littermate pairs of male weanling rats were placed in individual metabolic cages in a specially constructed chamber allowing standard air flow and temperature under conditions of low and high humidity. One of each pair was pair-fed Diet II, with the corresponding littermate receiving the fat-free diet (Diet I). Consecutive daily observations were made over a period of eight weeks. At low humidity (30% to 40%), insensible water loss in the fat-deficient group was about 600 to 800 ml. per square meter per 24 hours, in contrast to 300 to 400 ml. per square meter per 24 hours in the isocaloric controls. When the animals were transferred to high humidity (100%), the IWL in control animals fell to approximately 200 ml. per square meter per 24 hours, whereas very little change occurred in the IWL of fat-deficient animals. This is interpreted to indicate that the increased energy loss in fat deficiency does not primarily or predominantly derive from the simple physical process of increased water loss from the skin as a result of characteristic morphologic alterations. Other factors must, therefore, be taken into consideration: (1) hyperthyroidism (ruled out by work reported from this laboratory); (2) increased synthesis of fat; (3) deranged cellular oxidative mechanisms (e. g., uncoupling of oxidation and phosphorylation).

**Influence of Varying Amounts of Pyridoxine on Fat Deficiency and Oxygen Consumption.** RICHARD L. WALL, B.A.*; THEODORE C. PANOS, M.D., and HILDA F. WIESE, Ph.D.,* Galveston, Texas.

Rats deficient both in pyridoxine (vitamin $B_6$) and essential fatty acids are benefited by the administration of either pyridoxine or methyl linoleate. In addition, the sparing action of fat on vitamin $B_6$ deficiency appears to be well established. The influence of vitamin $B_6$ on fat deficiency is less clear, having been tested only on animals already deficient. The present experiment was designed to investigate the possible sparing effect of daily administration of large amounts of vitamin $B_6$ to weanling rats from the time they are placed on the fat-free diet. Male weanling rats were placed on the following diets: Group 1, fat-free without vitamin $B_6$, ad libitum; Group 2, fat-free with normal vitamin $B_6$ (5γ per gram of food), ad

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libitum; Group 3, fat-free with excess vitamin $B_6$ (125γ per gram of food), ad libitum; Group 4, "fat-free with fat" without vitamin $B_6$ (diet as in Group 1 but with cottonseed oil substituted for sucrose to provide 30% of available calories of fat); Group 5, "fat-free with fat" with normal vitamin $B_6$; Group 6, "fat-free with fat" with excessive vitamin $B_6$.

Groups 4, 5, and 6 were pair-fed isocalorically with Groups 1, 2, and 3, respectively. Observations of growth, activity, and skin changes were made frequently. Basal $O_2$ consumption was determined biweekly in eight animals from each group. After eight weeks all animals were autopsied and tissues and serum were taken for study.

The doubly deficient rats demonstrated the expected severe changes of debilitation, failure to gain, acrodynia, ear necrosis, and cheilosis. Pyridoxine-deficient rats receiving fat exhibited much less severe effects and, although fed isocalorically with the doubly deficient group, weighed 30% more. Prophylactic feeding of excess vitamin $B_6$ to fat-free rats did not significantly alter the development of deficiency manifestations, although the appearance of skin changes was slightly delayed. Basal oxygen consumption was significantly reduced in both vitamin $B_6$-deficient groups. It is particularly notable that the usually pronounced increased metabolic rate induced by fat deficiency was more than nullified by the concurrent vitamin $B_6$ deficiency as measured by oxygen consumption.

Vitamin $B_6$ deficiency was associated with relative enlargement of heart, kidneys, adrenals, thyroid, testes, and brain. Deficiency of both fat and vitamin $B_6$ caused a more pronounced enlargement of these organs as well as relative enlargement of the liver. Body fat was essentially totally lacking in the doubly deficient animals and remarkably reduced in those with pyridoxine deficiency. The addition of vitamin $B_6$ did not alter the usual organ-body weight relationships in fat deficiency previously described from this laboratory. Disturbances in serum lipid moieties characteristically observed in fat deficiency were not affected by administration of extra pyridoxine.

It is concluded that vitamin $B_6$ deficiency significantly reduces basal oxygen consumption, even in the presence of concomitant fat deficiency. The sparing action of fat on vitamin $B_6$ deficiency is confirmed. Prophylactic administration of excessive amounts of vitamin $B_6$ does not affect the development of the usual manifestations of fat deficiency.

**Ammonia Metabolism in Infants and Children.** JOHN A. ANDERSON, M.D., Ph.D., and ERMA v.O. MILLER, M.S.,* Minneapolis.

Patients with acute or chronic liver disease occasionally have elevations in the content of promptly diffusable ammonia in their blood. Central nervous system symptoms in such patients have been attributed in part to "ammonia intoxication." The majority of these observations have been made in adult subjects. Limited studies in infants and children are available.

The present study was designed to investigate several aspects of ammonia metabolism in infants and children. With use of the Conway microdiffusion method, observations on the following have been made: (1) the relationship of the content of ammonia in maternal blood to that in newborn cord blood; (2) the effect of $NH_4Cl$ administration to mothers on the ammonia content of maternal and cord blood; (3) changes in the ammonia content of blood during the newborn period; (4) effect of neomycin on ammonia content of blood in neonatal period; (5) the ammonia content of blood in erythroblastotic infants; (6) the relationship of the ammonia content of the blood to that in cerebrospinal fluid in normal children and in children with central nervous system disorders.

These studies indicate the following: It appears that the level of maternal venous blood ammonia is significantly higher than that of the venous cord blood of their infants and that elevations in the mother's blood by administration of $NH_4Cl$ cause increases ammonia in the infant's venous cord blood. The ammonia content in newborn venous blood at birth (0.51 micromoles $NH_3$ per milliliter ±0.016) rises promptly within 12 hours and reaches peak levels (0.90 micromoles $NH_3$ per milliliter ±0.15) by 48 to 96 hours. Return to normal values occurs by 120 hours. The administration of neomycin orally for the first six days of life prevents the ammonia rise in the blood of normal babies. Certain erythroblastotic infants may show increases in the ammonia content of the blood to levels comparable to those occasionally observed in patients with liver disease (1.43 micromoles $NH_3$ per milliliter), demonstrating central nervous system symptomatology. This rise may be present in spite of exchange transfusion.

No appreciable amount of ammonia is found in the cerebrospinal fluid of children having normal blood values. Elevations in the blood, due to disease or induced by $NH_4Cl$ administration, cause a rise of ammonia in cerebrospinal fluid.

It would appear from these observations that while the infant's cord blood ammonia level is lower than the mother's, increases in maternal blood are reflected by a rise in that of the infant. There appears to be, under normal conditions, a barrier to transfer of ammonia from blood to cerebrospinal fluid. When induced blood rises are present, transfer to cerebrospinal fluid occurs. The rise in the ammonia content of venous blood in the newborn period appears to be due predominantly to the evolution of bacterial flora in the intestinal

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tract. This may be due to persistence of the ductus venosus arantii between the portal and umbilical veins and the inferior vena cava. Transitory neonatal liver-function limitation must also be considered. The excessive rise in blood ammonia in certain erythroblastotic infants may also be due to intensification of both these factors; hepatic enlargement and parenchymal injury, as indicated by biopsy, have been observed. Central nervous system depression has been observed in three erythroblastotic infants with elevated blood ammonia values comparable to those found in adult patients with liver disease. Depression of the central nervous system in the erythroblastotic infant resembling early kernicterus symptomatology may be due in part to "ammonia intoxication," as one infant presenting such signs for several days following exchange transfusion appeared to be normal at 10 months of age.

**Achalasia of the Distal Rectal Segment with Normal Innervation of the Myenteric Plexuses of This Area.** MURRAY DAVIDSON, M.D.,* and CHARLES BAUER, M.D.,* New York. Introduced by SAMUEL Z. LEVINE.

Two years ago one of the authors (M. D.) described a gastrointestinal motility technique which could be of aid in establishing the diagnosis of congenital aganglionic megacolon by demonstration of achalasia in the distal rectum. The portion of distal rectum outlined by this method correlated with the segment demonstrated to be aganglionic in the surgically resected specimen.

This technique has proved useful in elucidating a variant of the classical clinical picture in three children with persistent obstipation and constipation from early in life. Unlike most patients with congenital aganglionic megacolon, these children had fecal soiling as a prominent symptom. Prior investigations had not established any diagnoses, and it was thought that they represented cases of psychogenic obstipation with associated fecal incontinence. Attempts at management with drugs, toilet training routines, and, in two of the children, with psychotherapy had all failed.

When first seen by us they were 5, 9, and 13 years of age, respectively. All had large fecal impactions. On rectal examination a short segment of terminal rectum (1 to 2 in.) was free of stool. Barium enema was not consistent with the diagnosis of congenital megacolon. However, motility study revealed differences similar to those seen in congenital aganglionic megacolon, between the patterns in the terminal rectal segment and more proximal colon.

After operation the terminal achalasic segment in each was demonstrated to have normal ganglia on pathologic study. Nevertheless, the patients experienced the "call to stool" for the first time in their lives and follow-up motility study displays a normal pattern. Clinical follow-up ranges from seven months to two and one-half years.

It is planned to review the technique of diagnosis; to present the clinical, pathological, and motility data on these patients, and to discuss the relationships between this entity and those of psychogenic obstipation and classical congenital aganglionic megacolon.

**Novobiocin in Common Pediatric Infections.** ANGELLA D. FERGUSON, M.D.,* and ROLAND B. SCOTT, M.D., Washington, D. C.

According to reports dealing mainly with adult patients, novobiocin, one of the newer antibiotics, has been found to be particularly effective against Micrococcus pyogenes (Staphylococcus). The purpose of this study was to determine the blood concentration of novobiocin after a single oral dose and to evaluate the drug clinically in the treatment of acute infections in children.

Single oral doses of novobiocin were administered to 12 subjects, and blood samples were taken at various intervals to determine the concentration of the drug. Although all blood concentrations were substantial, higher levels were obtained with the calcium salt than with the sodium salt. The latter derivative, however, seemed to be more palatable and was more acceptable to the children.

Of the 56 patients treated with novobiocin, 47 received the sodium salt of novobiocin and 9 received the calcium salt. Nineteen hospitalized children and twenty-eight children in the outpatient department received the sodium salt. Laboratory studies on the patients included novobiocin blood levels, liver-function tests, urinalyses, hemograms, and nose, throat, and blood cultures. The dosage employed was 20 mg. per kilogram of body weight orally per day in divided doses every six hours for both the sodium and calcium salts.

Of the 19 hospitalized patients treated with the sodium salt, 10 patients had pneumonia and 9 had bronchitis or other forms of upper respiratory tract infections. The average duration of fever in those with pneumonia was 27.6 hours; in the group with upper respiratory tract infections the average duration of fever was 22 hours. A good response to the drug was obtained in all patients except one outpatient, who had bronchopneumonia and acute gastroenteritis. There were no toxic or untoward reactions observed in any of the patients.

**The Leukocyte-Stimulating Factor in Rabbit Skin.** J. V. COOKE, M.D.†; DAVID GOLDRING, M.D.,* and L. KAHN, M.D.,* St. Louis. Introduced by ALEXIS F. HARTMANN SR.

The basic mechanism of leukocytosis remains unknown. Our approach is based upon the hy-

* By invitation.

† Dr. Cooke died June 29, 1956.

pothesis that one reaction by which leukocytopoiesis is initiated is through the elaboration of a substance by injured tissue. Since thermal injury to skin will result in leukocytosis, this tissue should be capable of elaborating a leukocyte-stimulating factor.

Such a substance was demonstrated by preparing extracts in Tyrode's solution of normal rabbit skin and injecting them subcutaneously into other rabbits. There was a reproducible response in well over 50 rabbits so tested which was characterized by an initial granulopenia of 75% below the initial base count and a granulocytosis of 200% above the base count in 48 hours.

When normal rabbit skin was subjected to heat of 65 C for one minute, the extract of such tissue contained very little of the leukocytopoietic effect.

When, however, such injured skin was incubated for 24 hours at 37 C in Tyrode's solution, there was evidence of intensification of the leukocytopoietic effect.

Preliminary studies have been conducted in an effort to study the nature of the substance and the following facts have been learned: 1. The factor is heat-labile and is destroyed when heated for one minute at 100 C. 2. The material is probably protein in nature because (a) it is nondialyzable; (b) it is precipitated by one-half and fully saturated $(NH_4)_2SO_4$; (c) its effect is destroyed by trypsin.

Further studies reveal that, in addition to the leukocytopoietic factor, two other substances are present in the skin extract; one produces a febrile response, and one, a granulopenic response four hours after administration. The granulopenic and pyrogenic factors are heat-stable and, therefore, can be separated from the leukocytopoietic factor. These substances are also dialyzable and precipitable by one-half and fully saturated ammonium sulfate, and their effect is destroyed by digestion with trypsin.

Subcutaneous administration of the skin extract to rabbits did not produce any local inflammatory response. This extract was also given to six human subjects, and in three there was a moderate local inflammatory reaction, fever, and a marked leukocytopoietic effect. Further studies are planned in an effort to define the chemical nature of these substances.

**Serum Transaminase Studies in Infants and Children.** MARTIN J. KAPLAN, M.D.,* and FELIX WRÓBLEWSKI, M.D.,* New York. Introduced by S. Z. LEVINE.

The use of serum enzymes, such as serum glutamic oxaloacetic transaminase (SGO-T) and and serum glutamic pyruvic transaminase (SGP-T), as an aid to the diagnosis of hepatic and myocardial disease in adults suggested that serum enzymes may be useful as an aid to clinical diagnosis in pediatrics.

The validity of these enzyme studies is based on the assumption that acute injury or necrosis liberates significant amounts of these enzymes from tissues and organs into the blood, where they can be measured.

The present study consisted of determining SGO-T and SGP-T activity in a series of full-term newborn infants and their mothers and in a group of infants and children with known hepatic disease and another group without known hepatic disease.

Analysis of the data collected revealed that newborns, infants, and children have different serum transaminase values than adults. The highest levels of serum enzymes tested were found in blood of newborn infants several hours after birth, with a gradually decreasing activity through infancy and childhood. The serum transaminase activity was normal in diseases without liver or muscle involvement, while it was increased in liver and muscular disease.

**Evaluation of the Blood-Cerebrospinal Fluid Barrier with Radioiodinated Serum Albumin.** LAWRENCE B. SLOBODY, M.D.; DOROTHY YANG, M.D.,* and MIRIAM LENDING, M.D.,* New York.

The permeability of the blood-cerebrospinal fluid barrier was evaluated by determining the rate of passage of albumin $I^{131}$ from plasma to cisternal fluid in animals under normal and hypoxic conditions.

The permeability of the membrane comprising the blood-cerebrospinal fluid barrier to any given substance at a fixed plasma concentration of that substance can be expressed in terms of the quantity passing from plasma to cerebrospinal fluid across a unit surface area per unit time under unit pressure difference. Normally albumin passes through the blood-cerebrospinal fluid barrier extremely slowly.

Albumin $I^{131}$, 3$\mu$c to 5$\mu$c per pound, was injected intravenously into dogs. Cisternal fluid and heparinized blood samples were then obtained at varying intervals. In 32 normal dogs, the concentration ratio of CSF radioactivity to plasma radioactivity was 50 to $70 \times 10^{-5}$ at the end of four hours.

In 31 dogs severe hypoxia was induced for periods of one-half to four hours with use of either nitrogen oxygen mixtures by endotracheal intubation or a Smith-Jones pressure chamber simulating altitudes of 25,000 to 35,000 feet. The albumin $I^{131}$, 3$\mu$c to 5$\mu$c per pound, was injected intravenously just prior to the induction of hypoxia. When hypoxia was maintained for one hour or longer, there was a marked increase in the

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concentration ratio, to 175 to 450×10⁻⁶ by four hours. The increase of CSF albumin $I^{131}$ concentration as a function of time for the hypoxic animals was about five times that of the control animals. In the hypoxic animals the concentration ratio was frequently higher by four hours than after 24 to 48 hours in normal animals.

It is concluded that severe hypoxia in dogs produces increased permeability of the blood CSF barrier to albumin. This method could be applied to the study of changes of permeability of the blood-cerebrospinal fluid barrier in clinical conditions.

**Unsaturated-Fat Feedings and Serum Cholesterol Levels in Infancy.** JULIUS POMERANZE, M.D.,* and ALTA GOALWIN, M.D.,* New York. Introduced by LAWRENCE B. SLOBODY.

There is evidence that atherosclerosis is in part related to an abnormality of lipid metabolism. The atherosclerotic process may be manifest in infancy and childhood.

In the adult, serum cholesterol levels can be lowered by a substantial reduction in the fat content of the diet. Even when the fat content remains high, an exclusively vegetable-fat diet can lower the serum cholesterol level in man. The degree of unsaturation of the vegetable oils apparently correlates with their depressing effect on serum cholesterol.

We studied (1) serial serum cholesterol levels from birth to 2 years of age in our normal infants and compared them with those reported in infants from countries where infant-feeding habits are different, (2) serial serum cholesterol levels in infants fed foods containing predominantly unsaturated fats; (3) weekly serum cholesterol levels in six infants to whose evaporated milk formula 50 gm. of corn oil was alternately added and removed at three-week intervals for a period of six months.

The following results were obtained: 1. In normal infants on the usual evaporated milk formula, serum cholesterol levels rise during the first six months of life from an average of 80 mg. to over 150 mg. per 100 cc. This is significantly different from those reported in the Italian literature. In Italian infants serum cholesterol levels do not similarly rise. 2. In infants fed substituted milk products with vegetable fats replacing animal fats, serum cholesterol levels did not rise. 3. Serum cholesterol levels fall when 50 gm. of corn oil is added to the evaporated milk formula and rise in the absence of the corn oil.

In this study we have begun to establish the relationship of serum lipid levels during infancy and childhood to diets modified in their fat content. The statistics derived from this and subsequent studies may help to clarify the problem of atherogenesis and lipid metabolism, especially in early life.

**Transfer and Duration of Naturally Occurring and Salk-Vaccine-Induced Maternal Antibodies in Newborns: Preliminary Observations on the Antigenic Potency of the Oral Attenuated Live-Virus Poliomyelitis Vaccine in Newborns and Young Infants.** MAURICIO MARTINS DA SILVA, M.D.*; JOHN L. MCKELVEY, M.D.*; KONALD A. PREM, M.D.*; HENRY BAUER, Ph.D.*; MARION K. COONEY, M.S.,* and EUGENE A. JOHNSON, Ph.D.,* Minneapolis. Introduced by JOHN A. ANDERSON.

These studies were designed to determine the extent and duration of transfer of naturally occurring and artificially induced (Salk vaccine) poliomyelitis antibodies to newborn infants. The capacity of orally administered attenuated live-virus poliomyelitis vaccine to modify congenitally acquired antibodies is being studied. Observations on the comparative effectiveness of intradermally versus subcutaneously administered Salk vaccine as well as differences in antigenic potency of Salk vaccine preparations have been made.

One hundred eighty-five pregnant women have been studied. One hundred thirty-five were given Salk vaccine either subcutaneously (two doses of 1.0 ml. at four-week intervals) or intradermally (two doses of 0.2 ml. at four-week intervals). Antibody titers were determined before vaccination and one month following completion of inoculation. Maternal and cord blood antibody titers were measured at birth. Successive antibody titers were determined at three-month intervals during the first year of life on all babies born of these mothers. Twenty-five infants (born of mothers immunized during pregnancy with Salk vaccine), ranging in age from 4 days to 6 months, were given living attenuated poliomyelitis virus Type 1 (SM strain). The stools of these infants and of the members of their families were examined for presence of virus by weekly stool cultures; associated changes in antibody titer were also noted. Sixty days after feeding Type 1, the infants were given Type 3 living attenuated poliomyelitis virus (Fox strain), and after another three weeks they were fed Type 2 attenuated virus (MEF$_1$ strain). Tissue culture techniques were used in all these studies.

Naturally occurring antibodies to all three recognized types of poliomyelitis viruses were present in 34% of 185 pregnant women tested. In 12% no poliomyelitis antibodies were detected when the serum was diluted 1:4. Salk vaccine produced significant antibody titers for all three types in 82% of mothers. Intradermal inoculation elicited as good an antibody response as the larger sub-

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cutaneous dose. The antigenic potency of Salk vaccine preparations varied.

The cord blood of each infant contained essentially the same antibody titer as the blood of his vaccinated mother. The "half-life" of Types 1, 2, and 3 antibodies present in the neonatal period was approximately one and one-half months, regardless of the level of the cord blood titers. Detectable antibody titers were present at 9 months of age in the great majority of infants whose antibody level at birth was 1:1024 or greater.

Preliminary data indicated good to excellent antibody response to all three types in 14 infants for whom antibody titers were available three weeks after completion of the oral vaccination with attenuated viruses.

Evidence for spread of Type 1 virus to other members of the family, as indicated by stool cultures, was found in six families, or 24% of the total. These families were large and characterized as being of low income level; overcrowding and poor hygienic practices were present in most of them. Similar studies for Types 2 and 3 are under way.

The biological characteristics of the viruses after one and more human passages are being evaluated and compared with those of the original strains.

The oral administration of attenuated live virus poliomyelitis vaccine to 25 newborns and young infants has been remarkably symptomless; no apparent clinical changes have been observed to date.

**Studies of the Immune Mechanism in the Newborn Period.** RICHARD T. SMITH, M.D.,* and ROBERT A. BRIDGES, M.D.,* Minneapolis. Introduced by JOHN A. ANDERSON.

The human infant at birth, and for a short time following birth, is apparently unable to initiate a primary immune response to a variety of antigenic stimuli. These studies represent attempts to gain insight into the mechanisms which govern the development of immunological maturity shortly after birth, by utilizing as an experimental model the response of the newborn rabbit to defined antigens. The results to date define a period of immunological immaturity lasting two to three weeks in the newborn rabbit, and they may be stated briefly as follows:

1. Rabbits failed to produce demonstrable antibody to bovine albumin (BSA) or γ-globulin (BCG), human γ-globulin (HGG), typhoid vaccine (TAB), or diphtheria toxoid, when these antigens were given at birth or during the first two weeks of life. Heterologous γ-globulin given at birth or shortly after birth was eliminated from the blood with a half-life value equal to that in adult rabbits, whereas heterologous albumin was eliminated at an extremely rapid rate, with a half-life value less than half that in adults.

2. Antigenic challenge with BSA at 2 weeks of age, or with smaller amounts of this antigen from 3 to 14 days, while not resulting in detectable antibody formation, appeared to inaugurate a primary immune response in a variable proportion of animals, since a secondary type response was elicited upon rechallenge at 60 to 90 days.

3. Injection of threshold amounts (10 to 200 mg.) of soluble heterologous protein antigens such as BSA, HGG, or egg albumin before 2 weeks of age resulted in a specific hiatus in the capacity of the animal to initiate an immune response to subsequent challenge with the antigen, which lasted 12 to 18 months. Attempts to induce a similar state of unresponsiveness with a variety of bacterial antigens have thus far been unsuccessful. Adult rabbits, which were immunologically unresponsive because of neonatal exposure, catabolized the heterologous protein at a rate similar to that of the analogous homologous protein. These animals did not develop delayed-type sensitivity to the antigen presented as a specific precipitate but supported the capacity of transplanted immune cells to produce the specific antibody. It was possible to "break through" the unresponsive state by presenting the specific antigen incorporated in Freund's adjuvants. A similar state of unresponsiveness to BSA has been produced in mice by neonatal injection of the protein.

4. Absorption of a single orally administered dose of 100 to 300 mg. of BSA in rabbits up to 5 days of age was sufficiently complete to induce a lasting state of specific immunological unresponsiveness in a high but variable proportion of animals. The question of whether smaller amounts given by this route produce a primary immune response is now being studied.

5. In confirmation of Dixon's recent observations, immune lymph node cells transferred to newborn rabbits have little or no capacity to produce antibody in experiments in which transfer of identical aliquots of cells to mature animals resulted in antibody formation.

The available data suggest that the immunological immaturity of the newborn rabbit is not absolute but must be defined in respect to each type and amount of antigen.

**The Use of a Standard Cell-Culture System to Test Antigenic Components of Hemophilus Pertussis Fractions Analyzed by Agar Diffusion Techniques.** HARRIET M. FELTON, M.D., D.Sc.(Med.)*; PIERRE GRABAR, Sc.D.,* and C. M. POMERAT, Ph.D.,* Galveston, Texas, and Pasteur Institute, Paris, France. Introduced by ARILD E. HANSEN.

The intact cells of Hemophilus pertussis have been shown to produce cytotoxic effects when

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brought into contact with living peritoneal macrophages. This tissue-cell system also seems to be useful for demonstrating the toxicity of certain fractions of these bacteria. On the other hand, certain other fractions which have been found to confer protection in animal tests produce very little cytopathology when introduced into this cell system. In an effort to define more accurately the characteristics of the protective antigen, experiments were initiated, using progressively more refined agar diffusion techniques, to demonstrate the results of the interactions between specific H. pertussis antisera and several fractions of the whole organism. Both the sonic extracts and the antisera were analyzed by a slightly modified agar diffusion technique of Ouchterlony and the agar immunoelectrophoretic analysis of Grabar and Williams. On the basis of these results, high-titered pertussis antisera were absorbed serially with sonic extract of H. pertussis.

The effects of a standard dose of sonic extract of H. pertussis on living cells that had been exposed to the absorbed sera have been demonstrated by means of perfusion-chamber experiments, and the results were recorded both by continuous time-lapse cinematography and by still photomicrography.

These investigations have been directed towards the characterization of the antigenic components of H. pertussis by certain physical means and correlation of these data with the results obtained by testing whole and serially adsorbed specific antisera with use of the techniques of dynamic cytopathology.

The results of the preliminary experiments to date indicate that a standard culture system of guinea pig macrophages is a sensitive indicator of the cytotoxic effects of intact cells of H. pertussis as well as of the toxic fractions of the organism.

Nontoxic fractions or "detoxified" whole bacterial cells do not produce the striking picture of damage that is seen with the more toxic agents.

This guinea pig macrophage-cell system has been used to demonstrate the protective effect of specific antisera produced in humans and animals by repeated inoculations of standard pertussis vaccines as well as by a more recent noncellular pertussis antigen. The preliminary results of the correlation of agar diffusion and agar immunoelectrophoretic analyses of certain fractions of H. pertussis cells as well as specific antisera, and the effects of these agents on a standard cell-culture system, suggest that these methods may provide a satisfactory assay system for the potency of pertussis antigens as well as the protective effect of pertussis antisera.

**Polio Virus Neutralizing Antibody Levels in Pediatricians and Preclinical Faculty Members.** PAUL F. WEHRLE, M.D.*; GERSON ARONOVITZ, B.A.*; ROBERT ZECHNICH, B.A.,* and PAUL PARKMAN, B.A.,* Syracuse, N. Y. Introduced by J. B. RICHMOND.

In an attempt to define further the conditions under which poliomyelitis virus is transmitted, two groups of persons of similar socioeconomic status were studied serologically. One consisted of 20 pediatricians on the voluntary and part-time staff of a medical school, while the other consisted of 20 scientists from the preclinical departments of the same institution. Both groups appeared to be similar in respect to age, sex, race, country of origin, travel out of this country, and period of residence in the community, as well as in regard to family size and extraprofessional contacts with children. The striking differences between the two were the frequent professional contacts with children in the home and office and the history of clinical management of poliomyelitis cases in the hospital by the group of pediatricians.

Serum samples from the two groups were obtained in July and November, 1956, and neutralizing antibody levels were determined at twofold dilutions of the paired sera. No significant changes in antibody titer were observed in either sample from those persons not immunized during the period of observation.

The distribution of initial antibody titers was almost identical in the two groups. Antibody was present somewhat more frequently among older persons. An association was observed between the presence of neutralizing antibody and the number of children in the family.

These data suggest that polio virus infection may not be readily acquired under normal conditions of pediatric practice. The presence of children in the household may be the important source of immunizing infections.

**Identification of Enteropathogenic Escherichia Coli by a Microprecipitin Method Specific for the B Antigen.** HELEN D. ZEPP, A.B.,* and HORACE L. HODES, M.D., New York.

More than 135 different O antigens are known among the Escherichia coli group. Approximately 15 of these types have been proven to be enteropathogenic, having caused sporadic and epidemic infantile diarrhea. It is not possible to identify these types except by serologic methods. Currently this is done by plating stools upon appropriate culture media and subjecting groups of E. coli colonies to slide-agglutination tests with pools of specific sera. This method has certain limitations, which can not be discussed here.

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So far as is now known, all E. coli types which are enteropathogenic contain a surface (or envelope) antigen of the B variety, 21 of which are known. A given B antigen is always associated with the same O antigen. Thus, when antigen $B_4$ is found it is always with an organism containing the O antigen 111, the organism being referred to as E. coli O111:$B_4$. It is probable that the B antigens are responsible for the diarrhea-producing capacity of the E. coli, and from the medical standpoint they are probably the most important antigens of these bacteria. Therefore, it would seem to be of importance to develop a practical method for identification of B antigens in order to obtain more significant data regarding enteropathogenicity than is furnished by determination of the O type of the E. coli present in stools.

We have developed a method for obtaining the B antigen in almost pure form. It is a mucoprotein-lipid compound. The method of extraction is based on the stability of the B antigen in boiling acetic acid. B antigen can be extracted directly from fecal matter or from an 18-hour broth culture inoculated with such material. The type of B antigen present can be identified by mixing a small amount of the extract with specific antiserum in a capillary tube. The resultant precipitin reaction is very clear-cut, and no cross reactions among the B antigens have been found. We believe this method to be of practical usefulness, giving more complete information than the colony isolation-slide agglutination method now in general use. The microprecipitin method gives information regarding the presence or absence of all enteropathogenic coli present in a stool, while from a practical standpoint it is not possible with the current slide agglutination technique to obtain this data regarding all 135 O types. The B antigen microprecipitin test can be carried out in any routine bacteriologic laboratory.

By a modification of the precipitin method we have demonstrated the occurrence of free B antigen in human blood. The presence of this antigen might prevent the demonstration of E. coli agglutinins in serum of infants recovering from E. coli infections. This might explain, in part, the apparent lack of production of specific E. coli antibodies by such infants.

**A New Amino Sugar Linkage in Streptococcal Cell Walls.** ALBERT DORFMAN, Ph.D., M.D., and J. ANTHONY CIFONELLI, Ph.D.,* Chicago.

Investigation of streptococcal cells harvested during active hyaluronic acid synthesis has revealed the presence of an array of fractions containing hexosamines and uronic acid. It has been possible to identify uridine diphospho-N-acetylglucosamine, uridine diphosphoglucuronic acid, and a uridine nucleotide containing another amino sugar. This amino sugar has also been found in the cell walls of streptococci. It appears to be identical with that isolated by Park from a nucleotide recovered from penicillin-treated staphylococci and by Strange and Powell, Salton, and Cummins and Harris from other bacterial cell walls. Chemical studies suggest it is a 3-substituted hexosamine containing an acid-stable linkage. This conforms the 3-O-α-carboxymethyl hexosamine structure suggested for the compound isolated by Strange from spores of Bacillus megatherium.

In view of the fact that cell walls of streptococci constitute the group-specific polysaccharide, it is apparent that this new amino sugar linkage is part of that substance. These findings suggest that the uridine nucleotide containing the substituted hexosamine is a precursor of the group-specific polysaccharide.

**Experimental Meningoencephalomyelitis Produced by Hemophilus Pertussis.** STANLEY L. WIENER, M.D.,* New York; MARY R. TINKER, M.A.,* and WILLIAM L. BRADFORD, M.D., Rochester, N. Y.

For the past three decades many attempts to reproduce encephalomyelitis experimentally on the basis of an allergic pathogenesis have been made, some with considerable success. Among the various methods used, injection of heterologous or homologous brain tissue with adjuvants, as described by Kabat, Wolf, and Bezer, is perhaps the most reliable. The adjuvant antigen usually employed is a mixture of brain tissue, oil, a dispersing agent, and a suspension of killed tubercle bacilli, because of its capacity to produce a delayed type of sensitization (the "Dienes effect").

This report describes the results of an experimental attempt to produce lesions in the central nervous system of the guinea pig by the injection of an adjuvant antigen containing killed Hemophilus pertussis.

*Methods and Materials.*—Animals: The Hartley strain of guinea pig was used because it has been reported to be highly susceptible to other forms of allergic encephalomyelitis. Fifty female guinea pigs, weighing from 350 to 450 gm. each, were assigned to five groups of 10 each.

Daily examinations were made for neurological signs, temperature, and weight. All surviving animals were killed 18 to 21 days after injection of the antigen.

The Antigen: The antigen was spinal cord tissue from the rabbit, previously shown capable of causing encephalomyelitis in the guinea pig in a dose of 0.08 mg. when injected as a part of the Freund antigen. The cord was stored at −5 C for three days prior to use.

The adjuvant consisted of a dried killed suspension of H. pertussis, Bayol F (paraffin oil), and an

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*Injections Given in Five Experimental Groups*

| Group | Phenol, Mg. | H. Pertussis, Mg. | M. Tbc., Mg. | Cord, Mg. | Bayol F+Arlucil A, Ml. |
|---|---|---|---|---|---|
| A | 0.5 | | | | |
| B | | 2.0 | | | 0.2 |
| C | 0.5 | | | 11 | 0.1 |
| D | 0.5 | 2.0 | | 12 | 0.1 |
| E | 0.5 | | 1.3 | 12 | 0.1 |

emulsifying agent (Arlucil A). The organisms were harvested after growth in the Cohen-Wheeler liquid medium and were preserved in the dry state.

The injections given each group are shown in the Table.

Each animal received two simultaneous intracutaneous injections (0.1 ml. each) of the proper material on its back.

*Results.*—None of the animals in the control groups (A, B, and C) developed abnormal temperatures, weight loss, or clinical signs of disease. In group D (H. pertussis) eight developed fever; nine, weight loss, and three showed neurological signs. Of these, eight showed pathological lesions of the brain.

In group E (tuberculosis) all 10 animals showed fever, weight loss, neurological signs, and lesions of the central nervous system.

*Pathology.*—All animals in group D (H. pertussis), except two, showed microscopic evidence of meningoencephalomyelitis. The commonest sites were the meninges, the subpial and subependyemal blood vessels, the tela choroidea of the third and fourth ventricles, and the choroid plexuses of the ventricles. The most frequent findings were lymphocytic perivascular infiltration and glial proliferation, choroiditis, meningitis, and the formation of glial nodules.

All animals in group E (tuberculosis) showed similar lesions.

*Conclusion.*—By intracutaneous injection of an adjuvant antigen containing killed whole H. pertussis organisms, lesions characteristic of meningoencephalomyelitis have been experimentally produced in the guinea pig. The course of the disease and the pathological findings were similar to those produced by injection of a similar antigen containing killed tubercle bacillus.

**Cataracts Following Mumps Virus Inoculation in Early Chick Embryos.** Russell J. Blattner, M.D.; Alice Polk Williamson, B.A.*; Lydia Simonsen, M.D.,* and G. Gordon Robertson, Ph.D.,* Houston, Texas.

Clinical reports dealing with the effect on the human fetus of German measles (rubella) in the mother have stressed the occurrence of congenital cataract. Experimental work on the developing chick embryo in this laboratory using Newcastle disease virus and influenza A virus showed that the structure of the developing eye, including the lens organ, is damaged, the extent depending upon method of virus inoculation, stage of development of the embryo, and virus titer of the inoculum. While these effects were definite, and have been amply confirmed, these virus infections in the embryo are lethal within 48 hours.

More recently, inoculation of the developing chick embryo with the Enders strain of mumps virus produced effects which were compatible with longer survival of the embryos after inoculation, and prominent in the findings was the presence of cataracts.

Cataracts were observed in a significant number of chick embryos inoculated at 48 hours of incubation with a high titer of mumps virus. The virus infection produced in such young embryos was eventually fatal, but cataracts were observed in embryos surviving from 3 to 15 days after inoculation. Other defects observed included general growth inhibition, retardation in development of the amnion, mild axis twists, retardation of feathering, defects of the choroid layer of the optic cup, and retarded development of the lids and skin around the eye. A decrease in the percentage of embryos showing defects was directly related to a decrease in the titer of the virus inoculated. Heat-inactivated mumps virus produced no cataracts or other defects. Virus was shown to increase in titer in the tissues of the embryos inoculated at such an early age. Microscopic examination of serial sections of the virus-infected embryo showed vacuolization and necrosis of the developing lens fibers.

**New Techniques in the Laboratory Diagnosis of Mumps and Its Complications.** Henry G. Crambletti, M.D.*; John P. Utz, M.D.*; Robert H. Parrott, M.D.*; Julius A. Kasel, B.S.,* and Clarence F. Szwed, M.S.,* Bethesda, Md. Introduced by Aims C. McGuinness.

A striking and, in our experience, distinctive cytopathogenic effect is observed when specimens containing mumps virus are inoculated into monkey kidney tissue-culture cells. The specimens also cause characteristic cytopathogenic changes in HeLa tissue-culture cells.

Primary isolations have been made repeatedly in tissue culture from saliva, from swabs of the

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mouth or orifices of Stenson's ducts, and, for the first time in our knowledge, from urine and cerebrospinal fluid. The percentages of recovery from the above sources from patients with clinical mumps are as follows: mouth swabs, 42%; saliva, 59%; urine, 36%, and cerebrospinal fluid, 40%. In our experience thus far, isolations have been made as early as the 2d day of illness and, in the case of urine specimens, as late as the 13th day of illness.

To establish that the cytopathogenic effect observed was due, in fact, to the mumps virus, the supernatant tissue culture fluid was studied in detail. Many of these fluids in the untreated state hemagglutinated chicken red cells. In others, concentration by ultracentrifugation was necessary to detect the hemagglutinins. This hemagglutinin was then shown to be inhibited by dilutions of antimumps guinea pig serum. In addition, the supernatant fluids have been shown to contain complement-fixing antigen when tested with antimumps guinea pig serum. Likewise, the cytopathogenic effect in tissue culture cells was shown to be neutralized by antimumps guinea pig serum. Convalescent sera from these patients with clinical mumps have, lastly, been shown to neutralize their own virus effect in tissue culture.

We fell that the tissue-culture techniques described for the diagnosis of mumps and its complications are superior to those employing chick embryos for the following reasons: 1. The need for a continuing supply of 7-day-old embryonated hens' eggs is eliminated. 2. Presumptive laboratory confirmation is usually available earlier when tissue culture is employed. 3. The tissue-culture methods are less expensive.

**Aldosteronism in a Nine-Year-Old Child.** NORMAN KRETCHMER, M.D., Ph.D.*; ANDREW DICKINSON, M.D.,* and RICHARD KARL, M.D.,* New York. Introduced by S. Z. LEVINE.

Usually, primary aldosteronism is characterized by hypertension, polyuria, polydipsia, tetany, muscular weakness, and paresthesias, associated with laboratory findings of hypokalemia, alkalosis, and hyposthenuria. More than 40 cases of this syndrome have been recognized since Conn's original description in 1955. An adrenal tumor was found in all the patients except the youngest, a boy, 17 years of age, who had bilateral adrenal hyperplasia.

This is a case study of a 9-year-old boy who came to The New York Hospital for an annual examination, at which time severe hypertension was discovered. The history was noncontributory except for persistent polyuria and polydipsia since infancy. There was blood pressure of 210/150, Grade II hypertensive retinopathy, and cardiac enlargement; no other clinical abnormalities were noted. Detailed laboratory studies were conducted over a six-month period. Significant laboratory findings were alkalosis, hypokalemia, hyposthenuria, normal 17-hydroxycorticosteroid and ketosteroid excretion, an excretion of 27γ of aldosterone in 24 hours, and reduced renal function as measured by inulin and *p*-aminohippurate.

On the basis of these results the patient was subjected to an exploratory laparotomy, and both adrenal glands were found to be grossly hyperplastic. In the course of two operative procedures, the entire left adrenal gland and approximately 90% of the right adrenal gland were removed. Microscopically there was hyperplasia of the zona fasciculata. Bilateral kidney biopsies showed pyelonephritis and some vacuolation of the proximal tubule cells.

Following surgery the blood pressure decreased to 140/90, and it has been maintained at this level. Aldosterone excretion now is 1.4γ/24 hours, and there is no evidence of hypokalemia or polyuria. The cardiac silhouette has returned to normal, and there has been a significant decrease in retinopathy. There remains an inability to concentrate urine and a reduced renal function. Despite removal of approximately 95% of the adrenal tissue, he does not require supplemental hormonal therapy.

This prepubescent child presented necessary criteria for the diagnosis of primary aldosteronism, which was associated with bilateral adrenal hyperplasia.

**Congenital Adrenal Hyperplasia and Rubeola: A Study of Three Fatal Cases.** LYTT I. GARDNER, M.D., and TYREE C. WYATT, M.D., Syracuse, N. Y.

This report describes three fatalities during rubeola in children with congenital adrenal hyperplasia. The children were aged 14 months, 7 years, and 8 years, respectively, with no history of sodium-losing episodes. The two younger children were female pseudohermaphrodites; the 14-month-old had never received any cortisone, and the 7-year-old was on medical therapy with cortisone. The oldest child was a boy with the hypertensive variety of congenital adrenal hyperplasia (previously reported by Shepard and Clausen, *Pediatrics* 8:805, 1951). He was receiving a very low dose of cortisone (25 mg. by mouth every other day). All three children died abruptly during the course of rubeola. The 8-year-old boy had a younger brother with the same adrenal syndrome who received γ-globulin prophylaxis and who successfully weathered modified measles under close medical supervision.

Autopsy studies were made on all three cases. There was no evidence of adrenal atrophy; in fact the adrenal glands were rather large (e. g., the

* By invitation.

boy's two adrenal glands weighed 62 gm). Histochemical studies revealed that there was almost complete depletion of the sudanophilic material in the adrenal cortices of the three children. These findings suggest that the adrenal cortices of these three children were undergoing maximal endogenous stimulation during the course of their measles. This is consistent with previous observations made on children during measles which support the concept that rubeola has an unusually potent ability to stimulate the adrenal cortex. It is also known that children with congenital adrenal hyperplasia show a paradoxical adrenal response to exogenous corticotropin (ACTH) (sodium loss rather than sodium retention). Thus it is conceivable that the intense stimulation of the adrenal cortex caused by measles may result in a specific response unfavorable to the patient with congenital adrenal hyperplasia.

The above situation is not to be confused with the fatal cases of chickenpox during cortisone treatment described by Haggerty and Eley (*Pediatrics* 18:160, 1956). In the chickenpox cases it would seem that there was suppression of adrenal function by cortisone in children with otherwise normal adrenal cortices. This is an entirely different metabolic setting from that found in the child with congenital adrenal hyperplasia who requires replacement treatment with cortisone or hydrocortisone. For this reason, no cross correlations should be drawn from the two groups of cases.

It is suggested that children with congenital adrenal hyperplasia who are exposed to rubeola receive modifying doses of γ-globulin and that they be hospitalized and observed with great care once they start coughing and become febrile in the course of the modified measles. They may need additional doses of cortisone or hydrocortisone above their ordinary daily dose requirement.

**Effect of Diethylstilbestrol on Growth and Skeletal Maturation in Adolescent Girls with Tall Stature.** GERTRUDE C. REYERSBACH, M.D.,* Boston. Introduced by ALLAN M. BUTLER.

In 1946 Albright gave diethylstilbestrol to a postmenarchal tall girl with open epiphyses in an attempt to stop further growth. During the four months of stilbestrol administration growth virtually ceased, but is was resumed after discontinuation of therapy.

With Dr. Albright's encouragement, the effect of diethylstilbestrol on six additional adolescent girls with predicted tall stature has been observed. These girls had no endocrine abnormalities. Breast development and pubic hair were present in all. Menarche had occurred in two. Diethylstilbestrol was administered continuously in doses of 5 or 10 mg. per day. In addition, progesterone (Pranone) was given at approximately 28-day intervals for a period of five days. This produced regular menstrual cycles.

The five premenstrual girls have been treated for periods of 8 to 29 months. The two postmenarchal girls were treated for a period of four months. Heights were carefully measured at monthly intervals. Films of the hand and wrist were taken at three- to five-month intervals for estimation of skeletal maturation. Except for the two postmenarchal girls, in whom treatment was only continued for four months, diethylstilbestrol has been given until the epiphyses appeared closed. In three girls, urinary FSH and pregnanediol determinations were done.

In two premenarchal girls in whom treatment has been completed the difference between predicted height and actual height has been 4.5 and 7.5 cm. This represents a significant reduction in their eventual height. In the three premenarchal girls still under therapy the same pattern is evident. The two postmenarchal girls treated for only four months showed no significant difference eventually in predicted and actual height, although during the course of treatment their growth ceased. Despite the interference in growth with regard to height, the rate of skeletal maturation was not significantly altered. During treatment urinary FSH was suppressed. Following cessation of therapy, normal periods were resumed immediately. Urinary pregnanediol was found, indicating ovulation. One patient had a normal pregnancy.

Possible modes of action of diethylstilbestrol in producing growth alteration without effecting skeletal maturation will be discussed. It seems, however, from these preliminary results that diethylstilbestrol given at an appropriate time in adolescent development is useful in curtailing growth in girls with predicted tall stature.

**Chromosomal Sex in Disorders of Sex Development.** MELVIN M. GRUMBACH, M.D.,* and WILLIAM A. BLANC, M.D.,* New York. Introduced by R. MCINTOSH.

Discovery of a sex difference in the interphase nuclei of somatic cells in man has provided a relatively simple method for assessing chromosomal sex. The application of this technique to the study of disturbances of embryonic sex differentiation has contributed to our understanding of these afflictions. It has also brought to light two conditions which previously had not been recognized as errors in sex development, namely, the syndrome of gonadal dysgenesis in chromosomal males and a congenital testicular disorder primarily involving the seminiferous tubules which we have called seminiferous tubule dysgenesis.

The sex chromatin pattern was determined in patients with various anomalies of sex mainly

* By invitation.

from oral mucosal smears and skin biopsies. In female pseudohermaphrodism, whether associated with virilizing adrenal hyperplasia or not, and in the classic forms of male pseudohermaphrodism the sex chromatin pattern agreed with gonadal sex. In true hermaphrodism, gonadal dysgenesis, and seminiferous tubule dysgenesis either male or female nuclei were found. Complete discordance between phenotypic and chromosomal sex was present in some patients.

More than 80% of patients with the syndrome of gonadal dysgenesis had a male chromatin pattern. Cytologic tests of sex are especially useful in the diagnosis of this condition in preadolescent girls before gonadotropin can be detected in the urine.

A female chromatin pattern was observed in nine patients with seminiferous tubule dysgenesis. Male nuclei were present in an 8-year-old boy with congenital anorchia and microgenitalia.

The bearing of these findings on the mechanism of normal and abnormal sex differentiation and on the classification of abnormalities of sex development will be discussed.

**Gynecomastia and Stromal Hyalinization in a Young Boy.** ALFRED M. BONGIOVANNI, M.D.*; WALTER R. EBERLEIN, M.D.*; BERNARD M. WAGNER, M.D.,* and IRIS T. JONES, M.D.,* Philadelphia. Introduced by JOSEPH STOKES JR.

A white boy aged 6½ years with gynecomastia since the age of 1½ years was referred to this institution for biopsy of the breast. The areolae were enlarged, measuring 1.5 cm. in diameter, and the protuberant breasts measured 5.0 cm. across the base. There were no signs of puberty. Numerous pigmented nevi were present on the limbs and trunk. Radiologic survey of the skeleton was normal. The possibility of hormone administration was excluded. The chromatin pattern of cells from the buccal mucous membrane was consistent with the male sex. Tissue from the breasts consisted mostly of hyalinized connective tissue. Testicular biopsy revealed a decreased number of tubules, some of which appeared to be atrophic and surrounded by a hyalinized stroma. The average tubular diameter was 60μ, and there was no significant coiling or tortuosity. Leydig cells were not identified. Occasional spermatogonia were noted. The normal testes for this age show a fibroblastic stroma and more tubules than were observed in this case. Examination of the urine revealed 0.9 to 1.0 mg. of 17-ketosteroids per day, 23γ to 31γ of estrogens (fluorometric) per day, and less than 4 m. u. gonadotropins per day. This may represent an early stage in false Klinefelter's syndrome and suggests that the condition may begin before the onset of puberty. Tubular hyalinization may appear later, with the rise in gonadotropins.

**Phallic Urethra in Female Pseudohermaphroditism.** WILLIAM A. REILLY, M.D.; FRANK HINMAN JR., M.D.,* and D. E. PICKERING, M.D.,* San Francisco.

The presence of a urethra coursing in a phallus, when the remainder of the external genitalia are equivocal for sex determination, poses a difficult diagnostic problem. The findings in eight female pseudohermaphrodite children (previously unreported) are described. There are 18 previously reported cases of phallic urethra in female pseudohermaphrodites; of the 24 cases, only 10 were due to adrenal cortical hyperplasia.

The etiology may be a blight resulting in a true congenital anomaly (4 cases). This may be an arrest about the time of formation of the phallic tubercle (so-called vaginal urethra type) or a more major fetal disaster, resulting in a gross anomaly which includes the external genitalia. A second cause of phallic urethra may be congenital adrenal hyperplasia (two cases). A third cause, similar in mechanism, may be intersexual development from androgens (one case) and from progesterone given to the pregnant mother (one case).

Chromosome analysis, hormone assays, urethrograms and vaginograms, urograms, gas insufflation, bone age, therapeutic cortisone trial, and even surgical exploration may be necessary to arrive at a definitive diagnosis.

* By invitation.

# Abstracts from Current Literature

## Acta pædiatrica, Stockholm

### 46, No. 2 (March) 1957


* Technique and Estimation of Oxygenation of the Human Fetus in Utero by Means of Hystero-Photography. B. Westin.—p. 117.
Staphylococcal Epidemiology in a Maternity Hospital. J. G. P. Hutchison and W. D. Bowman.—p. 125.
Chronic Idiopathic Autoimmune Hemolytic Disease in Childhood. A. Larson.—p. 144.
Gallengangmissbildung und Rhesus-Inkompatibilität. P. Paul.—p. 152.
On the Occurrence of Adenoviruses in Sweden. L. Kjellen, G. Sterner, and A. Svedmyr.—p. 164.
The in Vitro Glucose Uptake Inhibiting Effect of Body Fluids in Infantile Toxicosis. D. Bodá and S. Kiss.—p. 177.
Cirrhosis of the Liver in Two Children with Hyperproteinaemia. J. Bergstedt and C. Lingen.—p. 185.
Gastric Hemorrhagic Telangiectasia in a Child. G. Ehrenborg, I. Engstrom, N. O. Ericsson, B. Ihre, and B. Ivemark.—p. 191.
Ano-Rectal Abnormalities as a Congenital Familial Incidence. K. Kaijser and A. Malmstrom-Groth.—p. 199.
Monozygotic Twins, One with High Erythrocyte Values and Jaundice, the Other with Anaemia Neonatorum and No Jaundice. J. Bergstedt.—p. 201.
Changes in Body Water Compartments During Growth. B. Friis-Hansen.—p. 207.
Capillary Erection and Lung Expansion. S. Jaykka.—p. 208.
Proceedings of the Section of Pediatrics and School Hygiene of the Swedish Medical Society.—p. 210.


**Technique and Estimation of Oxygenation of the Human Fetus in Utero by Means of Hystero-Photography.**—An investigation of the state of oxygenation of the human fetus in utero by an ingenious technique involving direct observation and photography of the fetus, cord, and placenta is reported. Patients in whom therapeutic abortion was to be done were used, and observations were usually made when the length of gestation was 14 to 18 weeks. In accomplishing these investigations an instrument termed the hysteroscope was inserted into the uterine cervix after dilatation to Hegar 10; the membranes were then punctured, and the instrument was introduced into the sac, where direct observation and photography could be employed. Excellent color photographs of various structures were obtained, and from the comparison of colors with photographs taken after perfusion of cord vessels with blood of known oxygen saturation an estimation of oxygenation could be made. From the observations it was concluded that the oxygenation of cord blood was high; the fetus appeared pink, without visible cutaneous cyanosis, and the placenta appeared less cyanotic than after delivery. It was suggested that this hysteroscopic technique opens new possibilities for obtaining information concerning fetal physiology.

## American Heart Journal, St. Louis

### 53, No. 3 (March) 1957


* Three Patients with Congenital Pulmonic Stenosis Surviving for More Than Fifty-Seven Years. John B. Wild, John W. Eckstein, Eugene F. VanEpps, and James W. Culbertson.—p. 393.


### 53, No. 4 (April) 1957


Virus Myocarditis. W. J. Mogabgab.—p. 485.
* The Outlook for Children with Congenital Aortic Stenosis. Irvin B. Braverman and Stanley Gibson.—p. 487.
Total Anomalous Pulmonary Venous Drainage into the Portal Vein. Isadore Rosenfeld, Marvin L. Silverblatt, and Lotte Strauss.—p. 616.
Ventricular Parasystole in a Five-Year-Old Child. Randal E. Heinz and Frederic L. Eldridge.—p. 624.


**Three Patients with Congenital Pulmonic Valvular Stenosis Surviving for More Than Fifty-Seven Years.**—The authors present three patients with pulmonic valvular stenosis who survived into late adult life without experiencing any significant disability from their cardiac lesions. These patients are presented to illustrate the fact that pulmonic valvular stenosis may be compatible with an active life of normal longevity and that the diagnosis of pulmonic stenosis is not, in itself, an indication for surgical intervention.

The first of these patients enjoyed excellent health and performed hard manual labor until the age of 69 years, when he suffered a myocardial infarct which subsequently contributed to congestive failure and death. The second of these patients was a 57-year-old woman who had a variety of complaints but no objective evidence of disability. The third patient was a 57-year-old man who had had two episodes of loss of consciousness and several short periods of impaired consciousness, possibly related to the presence of pulmonary stenosis, but had otherwise been able to lead an active life. During his 57th year he was experiencing episodes of left upper precordial pain brought on by anxiety or strenuous exertion.

The diagnosis of valvular pulmonic stenosis was suspected clinically in one of the three patients and was established in all by cardiac catheterization. The maximum right ventricular pressure in the three patients was 105/10 mm. Hg, and the maximum systolic gradient across the pulmonary valve was 81 mm. Hg. The cardiac index was normal in the two patients in whom it was measured.

On the basis of their observations the authors conclude that a patient with pulmonic valvular stenosis may be expected to lead a reasonably active life until after middle age if he has (1) a nearly normal minute volume cardiac output at rest, (2) a right ventricular systolic pressure of 100 mm. Hg or less, (3) a normal pulmonary artery pressure, and (4) no symptoms referable to his heart anomaly.

**The Outlook for Children with Congenital Aortic Stenosis.**—The authors present a study of the course and prognosis of aortic stenosis in children. The study was based on the follow-up of 73 children in whom the clinical diagnosis of aortic stenosis (valvular or subvalvular) had been made on the basis of the classical signs of aortic stenosis—a loud harsh systolic murmur maximum in the first or second intercostal space at the right sternal border and a thrill palpable at the same location as the murmur, or in the suprasternal notch, or both. All of the patients were under the age of 16 years when the diagnosis was made, and all were thought to have congenital rather than acquired aortic stenosis. Two of the patients had an associated patent ductus arteriosus and three had associated coarctation of the aorta.

The ages of the 73 patients at the time of the follow-up study ranged between 3 months and 19½ years. Forty-one of the patients were without symptoms; twenty-six had symptoms, and six of the patients had died. All of those who had died were under the age of 16 years. Death was sudden in four of the six patients and was characterized by a very short terminal illness in the other two. Autopsies were performed in two of these six patients.

Previous reports have indicated that aortic stenosis is usually a well-tolerated lesion in children and that, although sudden death may result from this anomaly, the prognosis is usually good and symptoms do not usually appear until middle life. The fact that the mortality rate in this series was 8.2% and that 39% of the living patients had symptoms referrable to their cardiac lesion indicated to the authors that aortic stenosis in children may be a more lethal and incapacitating disease than had previously been suspected.

Experience with surgical correction of aortic stenosis in children is small, and the risk of this procedure is still to be evaluated. If surgical treatment of the defect proves to be relatively safe, it is apparent that some of the children with aortic stenosis should be operated upon. Assessing patients for the need of surgery, however, is not easy. On the basis of their experience, the authors conclude that all patients who have had syncopal attacks for which no other cause except aortic stenosis can be determined should be operated upon. Other features which suggest a need for surgery are the presence of easy fatiguability, electrocardiographic evidence of left heart strain, and cardiac enlargement on x-ray. Just how urgent an indication for surgery these latter symptoms and signs are is not clear. While these signs and symptoms were common in the patients who died, they also were found in the patients who continued to do well.

The authors suggest that with further surgical advances the mere presence of congenital aortic stenosis may be regarded as an indication for surgery but that, at the present stage of knowledge, those patients with syncope and easy fatiguability, cardiac enlargement, and marked left heart strain should be considered as surgical candidates.

## American Journal of Medicine, New York

22, No. 1 (Jan.) 1957

Cardiovascular Shunts. Milton Mendlowitz.—p. 1.

Multiple Myeloma and the Adult Fanconi Syndrome: I. Report of a Case with Crystal-like Deposits in the Tumor Cells and in the Epithelial Cells of the Kidney. Ralph L. Engle Jr. and Lila A. Wallis.—p. 5.

The Adult Fanconi Syndrome: II. Review of Eighteen Cases. Lila A. Wallis and Ralph L. Engle Jr.—p. 13.
Hydrothorax in Congestive Heart Failure. George A. Race, Charles H. Scheifley, and Jesse E. Edwards.—p. 83.
Hypochromic Anemia with Hyperferricemia Responding to Oral Crude Liver Extract. Daniel L. Horrigan, Richard M. Whittington, Russell Weisman Jr., and John W. Harris.—p. 99.
Agnogenic Myeloid Metaplasia: Its Natural History and Present Day Management. James W. Linman and Frank H. Bethell.—p. 107.
Emerging Concepts of the Structure and Metabolic Functions of Bone. W. F. Neuman and M. W. Neuman.—p. 123.
Salt-Losing Nephritis with Fixed Urinary Composition. Harvey C. Knowles Jr., Howard Levitin, and Albert Bridges.—p. 158.
* Lesions Resembling Vitamin B Complex Deficiency and Urinary Loss of Zinc Produced by Ethylenediamine Tetra-Acetate. H. Mitchell Perry Jr. and Henry A. Schroeder.—p. 168.

## 22, No. 2 (Feb.) 1957

* Kidney Function in Unilateral Pyelonephritis: I. Clinical Data. Alexander J. Michie and Catharine R. Michie.—p. 179.
* Kidney Function in Unilateral Pyelonephritis: II. Physiologic Interpretations. Alexander J. Michie, Catharine R. Michie, and Marie C. Ragni.—p. 190.
Coronary Arteriovenous Fistula: Clinical and Physiologic Report on Two Patients, with Review of the Literature. Raymond J. Walther, George W. B. Starkey, Evangeline Zervopulus, and Glen A. Gibbons.—p. 213.
The Electrocardiogram in Atrial Septal Defect: A Study of Twenty-Four Cases, with Observations on the RSR'$V_1$ Pattern. W. R. Milnor and C. A. Bertrand.—p. 223.
Incomplete Transposition of the Great Vessels with Biventricular Origin of the Pulmonary Artery (Taussig-Bing Complex): Report of Four Cases and Review of the Literature. Michele A. Chiechi.—p. 234.
Essential Hyperlipemia: Report of Four Cases, with Special Reference to Abdominal Crises. Leo J. Corazza and Ralph M. Myerson.—p. 258.
The Use of ACTH, Cortisone, Hydrocortisone and Related Compounds in the Management of Ulcerative Colitis: Experience in 180 Patients. Joseph B. Kirsner, Manuel Sklar, and Walter L. Palmer.—p. 264.
Calcium and Phosphorus Metabolism. D. Harold Copp.—p. 275.
Hemorrhagic Disease in Osteogenesis Imperfecta: Study of Platelet Functional Defect. Bernard M. Siegel, Irving A. Friedman, and Steven O. Schwartz.—p. 315.

**Lesions Resembling Vitamin B Complex Deficiency and Urinary Loss of Zinc Produced by Ethylenediamine Tetra-Acetate.**—An unusual reaction to ethylenediamine tetra-acetate (Versene; EDTA) occurred in two adults who were receiving the EDTA for its cholesterol-lytic effect. After three or four days of EDTA therapy (*2* or *3* gm. was given daily) the patients developed cheilosis, sore throat and tongue, a bright-magenta-colored tongue, and a dry scaly erythematous papular eruption. The findings suggested avitaminosis B; however, the patients were receiving added vitamins at the time of the reactions. The reactions cleared promptly on the withdrawal of EDTA, only to recur three to four days after the therapy was reintroduced. Studies of the urinary excretion of metals by these patients revealed a striking increase in zinc excretion, with lesser increases in the excretion of manganese and iron. Because of the similarity between the mucocutaneous lesions in these patients and those induced in pigs and rats by zinc deficiency, it is speculated that the disorder reported here is the consequence of zinc depletion secondary to chelation by EDTA.

**Kidney Function in Unilateral Pyelonephritis: I. Clinical Data; II. Physiologic Interpretations.**—The authors report differential renal-function studies of the diseased and the nondiseased kidney in patients with unilateral nonobstructive pyelonephritis. In five patients in whom chronic pyelonephritis had existed for less than six months, there was only slight decrease in the total renal function of the two kidneys combined, although there was significantly decreased function in the diseased kidney as compared with that of its mate. This indicates that a compensatory increase in function has occurred in the nondiseased kidney. That this increase in function is the result of glomerular hypertrophy and tubular hyperplasia is shown by the fact that glomerular filtration (GFR) and tubular function (measured by the $Tm_{PAH}$) increase in roughly parallel manner. Similarly, the decrease in function of the diseased kidney appeared to be predominantly the result of nonfunction of entire nephrons rather than selective injury to either glomeruli or tubules, since, again, the ratio of GFR to $Tm_{PAH}$ remained within normal range, while both GFR and $Tm_{PAH}$ were below normal. In five patients in whom the duration of chronic pyelonephritis had persisted for over six months, the total renal function of the diseased and nondiseased kidneys was significantly less than normal, indicating inability of the nondiseased kidney to balance the loss of function of its mate when pyelonephritis had been allowed to progress.

Studies of effective renal plasma flow (ERPF) in chronic pyelonephritis showed that, although the changes in ERPF were in the same direction as the changes in GFR and

$Tm_{PAH}$, the ratio of ERPH to $Tm_{PAH}$ was significantly below normal in both the pyelonephritic and the healthy kidney, thereby indicating relative ischemia of the remaining functioning nephrons. It is suggested that this relative ischemia is a consequence of increased intrarenal pressure secondary to parenchymal hypertrophy within a relatively inelastic capsule. In contrast, patients with acute pyelonephritis manifested renal hyperemia (increased $ERPF/Tm_{PAH}$).

The severity of renal dysfunction in patients with calculous pyelonephritis was minimal when there were staghorn or calyceal stones. Obstruction due to renal pelvic or ureteral stones, however, caused severe loss of renal function. Urterolithotomy in one case resulted in a four-fold increase in renal function, whereas removal of a staghorn calculus from another patient failed to cause improvement.

## American Journal of Pathology, Ann Arbor, Mich.

### 33, No. 2 (March-April) 1957


* The Nature of the Hyaline Thrombi in Thrombotic Thrombocytopenic Purpura. John M. Craig and David Gitlin.—p. 251.

* Variations in the Staining Characteristics of Human Fibrin. David Gitlin and John M. Craig.—p. 267.

A Differentiation of Certain Types of Fibrinoid and Hyaline. P. O'B. Montgomery and E. E. Muirhead.—p. 285.

A Study of Three Strains of Vaccinia Virus in Stable Cell Strain L, LLC-$M_1$, and HeLa. Fred W. Ryden and Charles C. Randall.—p. 293.

Nephrotic Glomerulonephritis. David B. Jones.—p. 313.

Hepatic Lesions in Sickle Cell Anemia. Y. S. Song.—p. 331.


**The Nature of the Hyaline Thrombi in Thrombotic Thrombocytopenic Purpura: Variations in the Staining Characteristics of Human Fibrin.**—In two cases, one typical of thrombotic thrombocytopenic purpura and the other somewhat less so, the intravascular hyaline thrombi reacted with fluorescein-labeled rabbit antihuman fibrin antiserum, but a negative reaction was obtained with antihuman platelet antibodies. Prominent features of the typical case were endothelial proliferation and the deposition of fibrin within the walls of nonoccluded vessels, appearing to be prethrombotic alterations. Traditional tinctorial methods for the demonstration of fibrin were negative or only occasionally and partially positive, but in artificial clot systems it was found that an albumin concentration of greater than 1 gm. per 100 cc. was necessary for positive histologic staining of the clots.

## Blood, New York

### 12, No. 1 (Jan.) 1957


Immunologic Features of Erythrocyte Sensitization: II. The Nature of Blood Group Antibodies. John H. Vaughan and Marion V. Waller.—p. 29.

Autoimmune Hemolytic Anemia: I. Analysis of Hematologic Observations with Particular Reference to Their Prognostic Value: A Survey of 57 Cases. William H. Crosby and Henry Rappaport.—p. 42.

* Erythrokinetics in Cooley's Anemia. Phillip Sturgeon and Clement A. Finch.—p. 64.

Clinical and Necropsy Findings in Hemoglobin C Disease. Wallace N. Jensen, R. Alan Schoefield, and Roy Agner.—p. 74.

Acquired Hypoprothrombinemia. Jessica H. Lewis, John H. Ferguson, Earle Spaugh, James W. Fresh, and Marjorie B. Zucker.—p. 84.


**Erythrokinetics in Cooley's Anemia.**—Studies of erythropoietic activity, red cell destruction, and rates of iron metabolism in four patients with Cooley's anemia are presented. Two of the patients studied had severe anemia; two cases were of the intermediate type. (One in each category had been previously splenectomized.)

The rate of red cell destruction was found to be 7 to 10 times normal both in the mildly anemic patients and in the one severely anemic patient in whom the $Cr^{51}$ studies were done. The authors point out, however, that this rate of red cell destruction would not be sufficient to produce severe anemia if compensatory increase in erythropoiesis, such as that usually found in other hemolytic anemia, occurred in Cooley's anemia. Therefore, studies of blood production were done to determine whether the major error in Cooley's anemia was in total hemoglobin production or in the effective delivery of red cells from the marrow to the circulating blood (termed, by the authors, effective red cell production).

Hemoglobin production was measured by study of marrow erythropoiesis, serum iron turnover, and urobilinogen excretion. Hemoglobin production by these measurements was found to be maximally increased in all four patients. Reticulocyte counts, red cell utilization of radioiron, and $Cr^{51}$ survival studies gave an indication of the actual delivery of cells from the marrow. A great difference was found here between the mildly anemic patients, with an

effective red cell production of four times normal, and the two severely anemic patients, who were unable to increase effective red cell production above that of normal nonanemic subjects.

It is concluded that the major defect in Cooley's anemia is not in total hemoglobin production but in the effective production of circulating erythrocytes. In severe Cooley's anemia most of the marrow activity is thought to be ineffective.

## Medical Journal of Australia, Sydney

### 2, No. 19 (Nov. 10) 1956

* Epidemiology of Tetanus in Queensland. D. W. Johnson.—p. 710.

### 2, No. 20 (Nov. 17) 1956

Congenital Heart Disease: Part I. General Survey, Methods of Investigation and Results of Surgery at the Alfred Hospital. C. J. Officer Brown, J. M. Gardiner, H. B. Kay, and K. N. Morris.—p. 741.
Congenital Heart Disease: Part II. Common Clinical Groups. H. B. Kay and J. M. Gardiner.—p. 746.
The Etiology of Mongolism, (an editorial comment).—p. 766.

### 2, No. 21 (Nov. 24) 1956

Experiences with Staphylococcal Infections in a Maternity Hospital. A. G. Mathew and C. Manessis.—p. 781.

### 2, No. 22 (Dec. 1) 1956

Acute Infections of the Ears in Children. Richard E. Dunn.—p. 821.
Acute Upper Respiratory Tract Infections in Childhood. S. E. J. Robertson.—p. 827.

### 2, No. 23 (Dec. 8) 1956

Afibrinogenaemia: Case Report of a Child with Recurrent Bleeding. Betty N. Wilson and Margaret R. Gutteridge.—p. 858.
Paediatric Society of Victoria (abstracts of papers presented).—p. 870.

### 2, No. 24 (Dec. 15) 1956

The Mortality of Childhood in Australia: Part I. Early Childhood. H. O. Lancaster.—p. 889.
Paediatric Society of Victoria (abstracts of papers presented).—p. 904.

### 2, No. 25 (Dec. 22) 1956

Management of Subnormal Children. A. G. Cumpston.—p. 917.
Management of Subnormal Children. E. M. Wann.—p. 918.
Malignant Disease in Childhood and Diagnostic Irradiation in Utero (an editorial comment).—p. 931.

**Epidemiology of Tetanus in Queensland.**—This is a report on the epidemiology of tetanus in Queensland, Australia, for a 10-year period, 1944 through 1953. The author notes that the incidence of tetanus in Queensland was approximately twice that expected on a population basis when compared with other areas in Australia. The total number of cases was 190. Ninety cases (47%) occurred in children under 15 years. This age group represents only 28% of the Queensland population. The portal of entry of infection was ascertained in 144 cases, and slightly more than half of these were puncture wounds. Lacerations caused 18%, and surgical procedures, another 12%. Of the total number of patients only 12 (7%) received antiserum prophylactically. The author stated that the dose was "usually inadequate." The over-all death rate was 47% and varied according to the incubation period. Mortality was 100% if the incubation period was less than five days. It was also noted that the death rate increased with the age of the patient.

## New England Journal of Medicine, Boston

### 256, No. 12 (March 21) 1957

The Hepatic Hilar Lymphatics of Man. A. H. Baggenstross and J. C. Cain.—p. 531.
Intrapericardial Interatrial Teratoma (Bronchogenic Cyst): Report of a Case Correctly Diagnosed and Successfully Removed. C. H. Dobbs, E. C. Pierce, and F. Rawson.—p. 541.
Entry of Bacteria Into the Urinary Tracts of Patients with Inlying Catheters. E. H. Kass and L. J. Schneiderman.—p. 556.

### 256, No. 13 (March 28) 1957

Diagnosis of Hypertension Due to Occlusions of the Renal Artery. E. G. Margolin, J. P. Merrill, and J. H. Harrison.—p. 581.
* Phenacemide in the Treatment of Epilepsy: Results of Treatment of 411 Patients and Review of the Literature. S. Livingston and L. L. Pauli.—p. 588.
Fatal Massive Necrosis of the Liver as a Manifestation of Hypersensitivity to Probenecid. E. S. Reynolds, R. C. Schlant, H. C. Gonick, and G. J. Dammin.—p. 592.
An Experiment in Maternal and Infant Care. S. B. Kirkwood.—p. 596.
Transaminase. F. G. Conrad.—p. 602.

**Phenacemide in the Treatment of Epilepsy: Results of Treatment of 411 Patients and Review of the Literature.**—The authors report on their experience with the use of Phenacemide (phenylurea) in the treatment of 411 patients with epilepsy. Their series was divided as follows: In 152 patients who had been receiving maximum doses of one or more anticonvulsants (phenobarbital, Mebaral, Gemonil, Dilantin, Mesantoin, Mysoline, Paradione, or Tridione) for at least six months and in whom the medication did reduce the frequency of the seizures to some extent, Phenacemide was added and the previous medication was continued at full dosage; in 146 others who had been on maximum dosage of drugs and in whom the drugs had been completely ineffective, Phenacemide was added, the previous medication being withdrawn gradually over the subsequent two or three months; 108 patients had had no previous medication and received only Phenacemide during the period of the study. There were 103 patients who had major motor seizures, 58 had pure petit mal, 125 had psychomotor seizures, 65 had minor motor seizures, and 60 had two or more of the various types of seizures. Ages of 322 patients ranged from 2½ to 14 years; 89 were over 15. Therapy ranged from six months to five years, with 198 having received the drug continuously for four or five years. Dosage was as follows:

| Age, Yr. | Dosage, Mg. |
|---|---|
| under 3 | 250 b. i. d., with maximum of 500 t. i. d. |
| 3-6 | 250 t. i. d., with maximum of 1,000 t. i. d. |
| 6-14 | 500 b. i. d., with maximum of 1,000 q. i. d. |
| Over 14 | 500 t. i. d., with maximum of 1,250 q. i. d. |

Essentially, significant benefit was obtained in patients with psychomotor seizures; 42% previously untreated were completely controlled, 30% previously treated and partially controlled by other drugs were completely controlled, and 16% previously treated with other drugs without any benefit were controlled by Phenacemide. Other forms of epilepsy were not significantly helped by Phenacemide.

No irreversible toxic effects were noted. Changes in personality and behavior (marked irritability, restlessness, belligerence, and depression) occurred in 15%. Suicidal tendencies have been reported in the literature. Hepatitis occurred in 1% to 5%. A few cases of rash, transient proteinuria, and gastrointestinal upset also occurred. No significant changes were noted in blood cell counts. The patient taking Phenacemide should be carefully watched for the undesirable effects.

## Pediatrics, Springfield, Ill.

### 19, No. 2 (Feb.) 1957

Changes in the Editorial Board of Pediatrics. C. D. May.—p. 171.

Salmonellosis in Infants and Children. W. A. Clyde Jr.—p. 175.

Salmonella Osteomyelitis Complicating Sickle Cell Disease. J. G. Hughes and D. S. Carroll.—p. 184.

Congenital Hypoplastic Anemia. H. A. Pearson and T. E. Cone Jr.—p. 192.

A Comparison of Oral and Intramuscular Benzathine Penicillin G for the Prevention of Streptococcal Infections and Recurrences of Rheumatic Fever. M. Markowitz, C. Ferencz, and A. Bonet.—p. 201.

Effect of Penicillins V and G on Carriers of Various Groups of Streptococci in a Children's Home. P. F. Wehrle, H. A. Feldman, and K. Kuroda.—p. 208.

Pulmonary Lesions of Newborn Infants: A Statistical Study. B. H. Landing.—p. 217.

Studies of Respiratory Insufficiency in Newborn Infants: I. Correlation of Tidal and Minute Volumes with the Trend of the Respiration Rates in Premature Infants. H. C. Miller and N. W. Smull.—p. 224.

Concentration of Fibrinogen in the Plasma of Normal Newborn Infants. P. M. Taylor.—p. 233.

* Blood Prothrombin, Proconvertin and Proaccelerin in Normal Infancy: Questionable Relationships to Vitamin K. J. W. Fresh, J. H. Ferguson, C. Stamey, F. M. Morgan, and J. H. Lewis.—p. 241.

Physicochemical Differences of Mucoproteins in Duodenal Fluid of Patients with Cystic Fibrosis of the Pancreas and Controls: Clinical Aspects. P. A. di Sant'Agnese, Z. Dische, and A. Danilczenk.—p. 252.

Sciatic Neuropathy in Infants Related to Antibiotic Injections. L. Scheinberg and M. Allensworth.—p. 261.

Pseudotumor Cerebri. R. B. Moore.—p. 266.

Serious Untoward Reactions to Therapy with Cortisone and Adrenocorticotropin in Pediatric Practice (Part II). R. A. Good, R. L. Vernier, and R. T. Smith.—p. 272.

Environmental Retardation (Hospitalism) in Infants Living in Families. R. W. Coleman and S. Provence.—p. 285.

A Play Program and Its Function in a Pediatric Hospital. V. B. Tisza and K. Angoff.—p. 293.

Facial Paralysis in Children: Review of the Differential Diagnosis and Report of 10 Cases Treated with Cortisone. R. S. Paine.—p. 303.

Pediatrics in India in 1955. P. Robinson.—p. 317.

Evolution of a Pediatric Society. H. Bakwin.—p. 325.

Certain Features of the Nutritional Value of Milk: A Tribute to Gail Borden: Borden Award Address. A. A. Weech.—p. 330.

**Blood Prothrombin, Proconvertin and Proaccelerin in Normal Infancy: Questionable Relationships to Vitamin K.**—Measurements of levels of prothrombin, proconvertin, and proaccelerin were made in blood specimens obtained from newly born infants and infants during the first few weeks of life. The case material was divided into the following groups according to administration of vitamin K:

I. Studies of the Cord Blood. Fifty-seven mothers received vitamin K within 48 hours prior to delivery, while 68 mothers did not.

II. Studies in Older Infants: Group 1, no vitamin K to either mother or child; Group 2, vitamin K, 10 mg. Synkayvite intramuscularly, to mother only, ante partum; Group 3, vitamin K, 5 mg. Synkayvite intramuscularly, to baby only at birth; Group 4, the above dosages of vitamin K both to mother ante partum and to baby at birth.

The results of these analyses indicate that, although wide individual variations are encountered, values for prothrombin and proconvertin are low at birth and tend to fall further within just two or three days of life, while values of proaccelerin are normal or above normal in all normal infants' bloods. After a few days of life there is a rise in levels of prothrombin and proconvertin, to be followed by a secondary "dip" occurring at a period of from 1 to 6 weeks of life. These variations appeared to be uninfluenced by the administration of vitamin K to either mother or baby.

In an effort to explain the fact that the one-stage "prothrombin time" gives consistently normal values in these infants, which have been demonstrated to be deficient in prothrombin and proconvertin, studies were made with a "synthetic plasma" in which proaccelerin was added in varying concentrations to plasma low in prothrombin and proconvertin, and one-stage clotting times were measured. These results showed that increasingly shorter clotting times were obtained with increased concentrations of proaccelerin, not leveling off at 100% ("normal") concentrations but continuing to be shorter at 200% and 300% concentrations. Since the values for proaccelerin in newborns was found to be 100% or more in all cases, it was suggested that perhaps this high level of proaccelerin maintains a physiologic defense against bleeding at this age despite low concentrations of prothrombin and proconvertin.

## Presse médicale, Paris

### 64 (Dec. 25) 1956

Osteodystrophic Syndrome with Gradual Osteolysis of the Bones of the Extremities, Associated with Vertebral and Costal Malformations. J. Marie, J. Salet, B. Leveque, and J. Sauvegrain.—p. 2173.

### 64 (Dec. 29) 1956

* Cerebral Component of Infantile Myxedema. J. Chaptal, P. Passouant, R. Jean, J. Cadilhac, and N. Carli.—p. 2257.

### 65 (Jan. 5) 1957

Antituberculous Activity of Sulfoniazide. M. Bariety and P. Choubrac.—p. 21.

### 65 (Feb. 9) 1957

Torsion of the Testicle in the Newborn. A. J. Bret and C. Coupe.—p. 253.

**Cerebral Component of Infantile Myxedema.**—Seventeen children aged 2 months to four years with congenital nongoiterous myxedema received several EEG studies in addition to clinical studies. Pure congenital myxedema with hypothyroidism or agencies of the thyroid showed slow maturation of the brain waves which improved with treatment, though more markedly with early treatment. In myxedema secondary to encephalopathy little improvement was noted in the EEG with treatment except in an occasional case. It was felt that tissue anoxia was responsible for the abnormalities in EEG noted with congenital myxedema and that this factor might also pay a role in myxedema secondary to encephalopathy.

## Radiology, Syracuse, N. Y.

### 68 (March) 1957

* Partial Obstruction of the Inferior Vena Cava by Herniation of the Liver Through the Foramen of Morgagni. David Rosenblum, Arnold Nussbaum, and Solomon Schwartz.—p. 399.

**Partial Obstruction of the Inferior Vena Cava by Herniation of the Liver Through the Foramen of Morgagni.**—A chest roentgenogram made soon after birth showed segmental atelectasis on the right lung, and the liver was palpable 4 fingerbreadths below the costal margin, and the spleen, 3. Later the hepatosplenonegaly regressed and the chest cleared. A repeat chest film showed abnormal configuration of the right heart border, and an addi-

tional film showed a mass in the right cardiophrenic angle. At 3 years of age evidence of mental deficiency was noted and a diagnosis was made of a herniation through the anterior medial portion of the diaphragm. A short kink in the inferior vena cava just beneath the diaphragm was observed by means of angiocardiography, with injection of 90% Hypaque into the right femoral vein. Preferential blood flow occurred through the paravertebral plexus, azygos system, and transhepatic collaterals, and the heart appeared to fill chiefly through the superior vena cava. At operation liver herniation and kinkage of the inferior vena cava was confirmed. A repeat angiocardiogram revealed no caval obstruction, and convalescence was uneventful.

The frequent coexistence of this type of herniation and mental deficiency is stressed. The authors believe it can best be explained on the basis of multiple congenital defects.

# News and Comment

## ANNOUNCEMENTS

**Postgraduate Course in Contagious and Communicable Diseases.**—The New York Medical College, Metropolitan Medical Center, announces a postgraduate course in the contagious and communicable diseases, under the direction of Harold Abramson, M.D., Professor of Clinical Pediatrics. The course will meet in thirty sessions, Nov. 6, 1957, to May 28, 1958, Wednesdays, 10 a. m. to 3 p. m. The fee is $300.00.

The course will consist of practical bedside instruction; ward rounds; laboratory and clinical procedures; lectures and seminars covering basic epidemiologic principles and newer advancements in the diagnosis, differential diagnosis, and treatment of children and adults with contagious and communicable diseases of bacterial, rickettsial, and viral origin. The course is designed for the pediatrician and the general practitioner.

Application should be made to office of the Dean, New York Medical College, 5th Ave. at 106th St., New York 29.

**National Foundation for Infantile Paralysis Postdoctoral Fellowships.**—Sept. 1 and Dec. 1 are the current deadlines for applications to the National Foundation for Infantile Paralysis for postdoctoral fellowships in research, academic medicine, or in the clinical fields of psychiatry, rehabilitation, orthopedics, the management of poliomyelitis, and preventive medicine. Applications for fellowships in the medical associate fields of social science, health education, physical therapy teaching, and occupational therapy teaching should also be filed by these dates. A spring date of March 1 is also provided.

Financial support of the Fellow varies according to his previous education, his professional experience, marital status, and number of dependents. Compensation to the institution is arranged according to the program undertaken. For a full academic program, tuition and fees are allowed; for other programs, a sum not to exceed $1250.00 per year (includes tuition) is provided.

All awards are made upon recommendation of the appropriate National Foundation Fellowship Committee. U. S. citizenship is required, but those who have filed a petition for naturalization will be considered. Partial fellowships are available for qualified veterans to supplement G. I. educational benefits.

Application must be received by March 1, Sept. 1, and Dec. 1 for consideration in May, November, and February, respectively.

**Postgraduate Courses in Pediatric Cardiology.**—Cook County Graduate School of Medicine announces two postgraduate courses in pediatric cardiology, Dec. 2-14, 1957. Two intensive postgraduate courses in pediatric cardiology will be offered. Each course will be of one week's duration and will be conducted under the supervision of Benjamin M. Gasul, M.D., Director of the Cardiac Division of Cook County Children's Hospital.

Course I, Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children, will start on Dec. 2. Course II, Roentgenology, Electrocardiography, Angiocardiography, and Catheterization, will begin on Dec. 9.

For descriptive circulars and application forms address: Registrar, 707 S. Wood St., Chicago 12.

## SOCIETY NEWS

**American Pediatric Society Meeting.**—The 67th Annual Meeting of the American Pediatric Society was held at Carmel, Calif., on June 19, 1957.

The following candidates were elected to active membership in the Society: Dr. Robert H. Alway, San Francisco; Dr. John B. Bartram, Philadelphia; Dr. Alfred M. Bongiovanni, Philadelphia; Dr. David H. Clement, New Haven, Conn.; Dr. Wallace W. McCrory,

Philadelphia; Dr. Gerald Miller, Rochester, N. Y.; Dr. Rosa Lee Nemir, New York; Dr. Edward F. Rabe, Danville, Pa.; Dr. Helen Reardon, Philadelphia; Dr. Harry Shwachman, Boston; Dr. Henry K. Silver, New Haven, Conn.; Dr. Genevieve Stearns, Iowa City.

The following members were elected as officers of the Society for 1957-1958: President, Dr. A. Ashley Weech; Vice-President, Dr. Alton Goldbloom; Secretary-Treasurer, Dr. Aims C. McGuinness; Recorder-Editor, Dr. Stewart H. Clifford; Member of the Council, for a seven-year term, Dr. Edward L. Pratt.

Dr. Irvine McQuarrie was selected as the 1958 Howland Medalist.

A special Committee in Education—with rotating membership—was appointed to advise the Society on matters concerning pediatric education. The membership and tenure of the members of this committee are as follows: Dr. Rustin McIntosh, Chairman, two years; Dr. Lee Forrest Hill, one year; Dr. Milton J. E. Senn, three years; Dr. Robert A. Aldrich, four years; Dr. Robert J. McKay, five years.

Schedule of future meetings: 1958, Hotel Traymore, Atlantic City, N. J., beginning Thursday morning, May 8; 1959, The Inn, Buck Hill Falls, Pa., beginning Monday morning, June 15.

## GENERAL NEWS

**Specialists Certified by the American Board of Pediatrics, Inc.**—The following physicians were certified by the American Board of Pediatrics, Inc., in San Francisco, June 21, 22, and 23, 1957.

Ainger, Lorin Eugene, Salt Lake City.
Apthorp, James S., Reseda, Calif.
Auerback, Marvin Lawrence Allen, San Francisco.
Avant, James Adaire, Jr., LeGrande, Ore.
Baker, Helen Thomas, Seattle.
Bertolin, Ralph Johnson, Olympia, Wash.
Bishop, Eugene Lindsay, Jr., Nashville, Tenn.
Bolter, Arthur, Castro Valley, Calif.
Bonney, Holbrook, Los Angeles.
Brainerd, Walton Kirk, Sacramento, Calif.
Breit, Arnold J., San Mateo, Calif.
Brown, George Walter, Mesa, Ariz.
Chiu, Dorothy, Burbank, Calif.
Clark, Ezra T., Danville, Calif.
Cohen, Nathaniel M., Jr., Costa Mesa, Calif.
Collier, Ella Mary, Oakland, Calif.
Curtis, John Abbott, Great Falls, Mont.
Delhotal, Charles E., Oklahoma City.
Diller, Howard A., Walnut Creek, Calif.
Edworthy, James Malcolm, Kamloops, British Columbia, Canada
Fogel, Harold Norman, Pittsburg, Calif.
Gaines, Jack W., Reseda, Calif.
Grunwaldt, Edgar, Monterey, Calif.
Hammond, Denman, San Francisco.
Hammond, E. Wylda, Eldridge, Calif.
Hansen, Russell Robert, Woodland, Calif.
Haskin, David, San Francisco.
Hazeltine, Frederick G., Seattle.
Herschel, Paul E., III, El Cerrito, Calif.
Hodgman, Joan Elizabeth, San Gabriel, Calif.
Holzman, Earl E., Pacific Palisades, Calif.
Hutchings, John Joseph, San Francisco.
Ibsen, Maxwell, San Jose, Calif.
Jack, Olive, Napa, Calif.
Jensen, Warren Pay, Bremerton, Wash.
Johnson, Walfred Wallace, Seattle.
Kanter, Albert J., Sunnyvale, Calif.
Kaplan, Charles B., Yuma, Ariz.
Koch, Richard, Los Angeles.
Kohn, Jean Gatewood, Burlingame, Calif.
Koulischer, Nina, San Francisco.
Krueger, Keith Vernon, Long Beach, Calif.
Lasker, Burton H., Reseda, Calif.
Lebovitz, Joseph L., Norwalk, Calif.
Leonards, Laurie Nicolas Richard, San Francisco.
Lewis, Donald, Seattle.
Linde, Leonard M., Los Angeles.
McCluskey, William Richard, Los Angeles.
Macfarlane, David W., Portland, Ore.
Marshall, Robert Henry, North Hollywood, Calif.
Martini, Mario Michael, Pacific Palisades, Calif.
Mason, James Cameron, Bellingham, Wash.
Mendelsohn, Eugene Sheldon, Napa, Calif.
Mendelsohn, Mary G. R., Napa Calif.
Meyer, John Frederic, Covina, Calif.
Mitchell, Donald Davis, Bellaire, Texas
Neal, William S., San Rafael, Calif.
Noonan, James William, Arcadia, Calif.
O'Gara, Louis A., San Francisco.
O'Neill, Richard M., San Jose, Calif.
Paulus, John L., Redlands, Calif.
Pew, Wilmer L., Eugene, Ore.
Richanbach, Henry S., Burlingame, Calif.
Romans, Robert M., North Hollywood, Calif.
Rothell, Fred B., Redondo Beach, Calif.
Rozgay, Clarence E., Seattle.
Russell, Melvin Gray, Jr., Dallas, Texas
Schellhase, Sybil Jean, Concord, Calif.
Schulz, Jeanette, Alton, Ill.

Schwarzer, Sigmund, San Bernardino, Calif.
Skinner, Alfred Loring, Mercer Island, Wash.
Smith, David W., Los Gatos, Calif.
Smith, Esmond S., Encino, Calif.
Smith, Sidney, Los Angeles.
Specht, Elmer E., San Mateo, Calif.
Stanford, David E., Redding, Calif.
Sult, Francis Laurance, Nampa, Idaho
Tanbara, George Ayao, Tacoma, Wash.
Thistlewaite, Edward A., Alhambra, Calif.
Tooley, William H., Berkeley, Calif.
Torello, Edward W., Jr., Burlingame, Calif.
Tower, John Cramton, Anchorage, Alaska
Wagner, Beverly Groat, Sacramento, Calif.
Wiener, Jacob J., Saint Albans, N. Y.
Wilson, Miriam G., Los Angeles.
Zamvil, Louis, Palo Alto, Calif.

The following physicians passed their examination in New Orleans, in February 1957, but were not eligible to receive certificates until July 1, 1957.

Cleveland, William W., Miami, Fla.
Coley, Elwood Brogden, Henderson, N. C.
Estrada, Ramiro P., San Antonio, Texas
Goldsmith, Richard William, Fort Leavenworth, Kan.
Ivey, John Francis, Jacksonville, Fla.
Kramer, John C., Tulsa, Okla.
Moore, William Locke, Greensboro, N. C.
Orgeron, Eugene B., Port Arthur, Texas
Polo, de Hilda Martinez, Hato Rey, P. R.
Rubinstein, Jack Herbert, Cincinnati.
Young, Roy Godfrey, Jr., Birmingham, Ala.

Special foreign certificates:
Barnes, Felino V., Manila, Philippines
Champion, Maret, Sydney, New South Wales, Australia
Desai, Krishnakant, Hiralal, McCain, N. C.
Hashim, Abdul Sahib, Springfield, Ohio
Mitra, Nirmal Kumar, Kansas City, Mo.
Rama Row, Garuda Venkata, Baltimore.
Reis, Antonio Dennis, Quezon City, Philippines
Sibinga, Maarten Smit, New York.
Teran, Jose Maria, Managua, Nicaragua
Valido, Constantino L., Cincinnati.
Ziai, Mohsen, Boston.
Evans, Audrey E., Boston.

# Books

## BOOKS RECEIVED

**The Riddle of Stuttering.** By C. S. Bluemel. Price, hard bound, $3.50; paper bound, $1.50; therapy records (4), $3.00. Pp. 142. The Interstate Printers & Publishers, Inc., Danville, Ill., 1957.

**A Visit to the Hospital.** By Francine Chase. Price, $1.50. Pp. 68, with 68 illustrations (one on each page). Grosset & Dunlap, Inc., 1107 Broadway, New York 10, 1957.

**Child Health and Development.** Edited by R. W. B. Ellis. Second edition. Price, $6.75. Pp. 525, with 81 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1957.

**The American Fluoridation Experiment.** By F. B. Exner and G. L. Waldbott. Price, $3.75. Pp. 277. Devin-Adair Co., 23 E. 26th St., New York 10, 1957.

**The Physiology and Biochemistry of Lactation.** By S. J. Folley. Price, $3.75. Pp. 153, with numerous illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

**J. A. M. A. Clinical Abstracts 1957.** Selected by I. Phillips Frohman. Price, $5.50. Pp. 564. Intercontinental Medical Book Corp., 381 Fourth Ave., New York 16, 1957.

**Venous Angiocardiography.** By Gasul et al. Price, $3.50. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

**The Mentally Ill Child: A Guide for Parents.** By Steven B. Getz and Elizabeth Lodge Rees. Price, $3.50. Pp. 88. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

**The Concept of Development.** Edited by Dale B. Harris. Price, $4.75. Pp. 287. University of Minnesota Press, Minneapolis 14, 1957.

**Modern Problems in Pediatrics: Vol II.** Edited by A. Hottinger and F. Hauser. Price, 32 francs. Pp. 222, with 89 illustrations. S. Karger AG., Arnold Böcklinstrasse 25, Basel, Switzerland, 1957.

**The Early Detection and Prevention of Disease.** Edited by John P. Hubbard. Price, $7.50. Pp. 350. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

**The Fight for Fluoridation.** By Donald R. McNeil. Price, $5.00. Pp. 241. Oxford University Press, 114 Fifth Ave., New York 11, 1957.

**Perinatal Loss in Modern Obstetrics.** By Robert E. L. Nesbitt Jr. Price, $12.50. Pp. 432, with 108 illustrations, including 10 in color. F. A. Davis Company, 1914-1916 Cherry St., Philadelphia 3, 1957.

**A Synopsis of Children's Diseases.** By John Rendle-Short. Price, not given. Pp. 624. John Wright & Sons, Ltd., 42-44, Triangle West, Bristol 8, England, 1957.

**An Atlas of Cardiac Surgery.** By Jorge A. Rodriguez. Price, $18.00. Pp. 250, with numerous illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

**Annual Review of Medicine: Vol. 8.** Edited by David A. Rytand and William Creger. Price, $7.00. Pp. 530. Annual Reviews, Inc., Grant Ave., Palo Alto, Calif., 1957.

**Childhood and Adolescence: A Psychology of the Growing Person.** By L. Joseph Stone and Joseph Church. Price, $6.50 (text price, $5.00). Pp. 456, with 18 illustrations. Random House, 457 Madison Ave., New York 22, 1957.

**Certain Language Skills in Children (Child Welfare Monograph Series, No. 26).** By Mildred C. Templin. Price, $4.00. Pp. 183, with 80 tables. University of Minnesota Press, Minneapolis 14, 1957.

**Handbook of Speech Pathology.** Edited by Lee Edward Travis. Price, $12.00. Pp. 1088, with numerous illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

**The Rehabilitation of Speech.** By Robert West, Merle Ansberry, and Anna Carr. Third edition. Price, $7.50. Pp. 676, with 53 illustrations. Harper & Brothers, 49 E. 33d St., New York 16, 1957.

**Endocrine Disorders in Childhood and Adolescence.** By Lawson Wilkins. Second edition. Price, $17.50. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

**Ciba Foundation Colloquia on Endocrinology: Vol. X. Regulation and Mode of Action of Thyroid Hormones.** Edited by G. E. W. Wolstenholme and Elaine C. P. Millar. Price, $8.50. Pp. 307, with 114 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1957.

**Ciba Foundation Symposium on the Chemistry and Biology of Purines.** Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $9.00. Pp. 327, with 124 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1957.

**Methodology of the Study of Ageing: Vol. 3 (Ciba Foundation Colloquia on Ageing).** Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $6.50. Pp. 202, with 47 illustrations. Little, Brown & Company, 34 Beacon St., Boston, 1957.

## BOOK REVIEWS

**Patterns of Mothering.** By Sylvia Brody. Price, $7.50. Pp. 446. International Universities Press, 227 W. 13th St., New York 11, 1956.

That there continue to be major gaps in our knowledge of personality development is apparent with each new case of an emotionally disturbed child that presents itself. The increasing incidence of seriously disturbed children, wherein the behavior is so atypical as to suggest a diagnosis of psychosis, sharply points up the need for a better knowledge of such development.

This book is a major and serious attempt to unravel a piece of this personality development. It is based on an infancy research project carried out at the Menninger Foundation between 1949 and 1950 under the direction of Drs. Sibylle Escalona and Mary E. Leitch. The essential material was drawn from a cross sectional examination of the behavior of 128 individual infants as observed in the care of their mothers for an approximately four-hour period by three investigators. Sixteen infants, eight boys and eight girls, were observed at monthly age levels from 4 through 32 weeks of age, both in their homes and in some special quarters arranged for this observation.

The bulk of the text is taken up with the very detailed presentation of the observations of the authors. But the book contains much more than this. The first two chapters are packed with a study of the literature concerning infant development and the maternal role in this process. It is as comprehensive a bibliography as possible, and it alone almost provides a justification for the book.

Following the description of the project, the authors have rated mothers on their sensitivity to the baby's needs, their consistency in dealing with the child, and the various frequencies of actions relative to handling, feeding, cleaning, and general care. It is of some interest that the observations lead to a conclusion that one of the major differentials in the care of children has to do with handling behavior, as much as it has to do with actual feeding behavior. This bears out previous observations on humans and animals that the bases of infant personality are set up extremely early in life through interpersonal contacts between child and mother, with feeding procedures only adding to the other elements of handling.

The author concludes the book with a series of chapters concerned with the psychoanalytic development of the ego, comparing this material with the data actually observed. The chapters are meaty and serious, and they warrant intensive reading.

The final chapter concerns the application of the observations to developing a working typology of mothers, as well as trying to relate the behavior of infants to various kinds of mothering. This chapter gives valuable clues as to the kind of maternal behavior to be expected from certain groups of mothers and suggests what sort of mothers of the future will derive from such handling. It is not a book to be read lightly, but one which may prove a landmark in thinking about maternal care.

Since the pediatric job is so largely concerned with assisting mothers, the valuable guides given in this text may well serve as a means of learning about such maternal behavior and the ways in which it can be modified to be of most assistance to the child.

The book is chiefly recommended as a major source book for data concerning these very early days of infancy and the development of the relationship between the mother and her child. There remains a considerable gap between the concrete data in this book and any preventive guides, but the material is set down and available for those who wish to use it.

**Diabetes Mellitus.** By T. S. Danowski. Price, $13.50. Pp. 510, with 26 figures and 26 tables. The Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

Those physicians who include juvenile diabetics among their charges will do well to have a copy of this book on their shelves. Dr. Danowski has drawn on his large personal experience in treating childhood diabetes and thorough understanding of the underlying metabolic defects in presenting an impressive compendium of facts. Since so many aspects of the pathogenesis and treatment of this disease are still controversial, the reader is briefly informed of the nature of the controversy and referred to an exhaustive bibliography. In general, the author has avoided extremes in his own recommendations, and his suggestions for therapy no doubt will find wide acceptance.

The volume is essentially a source-book of information providing the answers to almost any question which may be posed by the physician or his patient. The subjects covered include intermediary metabolism, the relation of the endocrine glands to diabetes, and experimental diabetes. The standard tests of carbohydrate metabolism are described in detail with their interpretations, and therapy and complications are discussed. The oral preparations recently made available as well as the newer insulins are considered, and, as is to be expected, there is also a good chapter on hydrogen ion regulation.

**Proceedings of The Third National Cancer Conference.** Sponsored by American Cancer Society, Inc., and National Cancer Institute, U. S. Public Health Service. Price, $9.00. Pp. 961, with numerous illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1957.

This book is a report on the conference consisting of six lectures and numerous symposia and panels on various types of cancer and various aspects. It is essentially a compilation of different persons' experiences in the treatment, diagnosis, and causation of cancer of different types. Although not in detail, there is good expression of each person's ideas and work.

It gives the worker in the field the varied opinions of good researchers and clinical workers. It will enable the practitioner to appreciate the many differences of opinion, but it is not meant to be a textbook or a complete discussion of any one subject.

The subjects covered are cancer of the breast, prostate, lung, head and neck, female genital tract, and gastrointestinal tract; the lymphomas and leukemias; chemotherapy in cancer; end-results in the treatment of cancer, and lectures on epidemiology, radiation neoplasia, virus etiology, chemical effects of growing tumors, the host with special reference to man, factors influencing the curability of cancer, and the measurement of morbidity.

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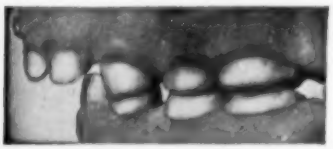

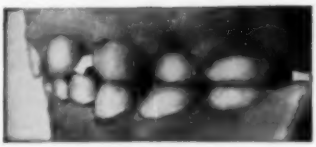

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